Decision Memo for Carotid Artery Stenting (CAG-00085R)

Decision Summary

The Centers for Medicare and Medicaid Services (CMS) has determined that the evidence is adequate to conclude that carotid artery stenting (CAS) with embolic protection is reasonable and necessary for the following:

- 1. Patients who are at high risk for carotid endarterectomy (CEA) and who also have symptomatic carotid artery stenosis \geq 70%. Coverage is limited to procedures performed using FDA approved carotid artery stenting systems and embolic protection devices;
- 2. Patients who are at high risk for CEA and have symptomatic carotid artery stenosis between 50% and 70%, in accordance with the Category B IDE clinical trials regulation (42 CFR 405.201), as a routine cost under the clinical trials policy (Medicare NCD Manual 310.1), or in accordance with the National Coverage Determination on CAS post approval studies (Medicare NCD Manual 20.7);
- 3. Patients who are at high risk for CEA and have asymptomatic carotid artery stenosis > 80%, in accordance with the Category B IDE clinical trials regulation (42 CFR 405.201), as a routine cost under the clinical trials policy (Medicare NCD Manual 310.1), or in accordance with the National Coverage Determination on CAS post approval studies (Medicare NCD Manual 20.7).

Patients at high risk for CEA are defined as having significant comorbidities and/or anatomic risk factors (i.e., recurrent stenosis and/or previous radical neck dissection), and would be poor candidates for CEA in the opinion of a surgeon. Significant comorbid conditions include but are not limited to:

- congestive heart failure (CHF) class III/IV;
- left ventricular ejection fraction (LVEF) < 30%;
- unstable angina;
- contralateral carotid occlusion;
- recent myocardial infarction (MI);
- previous CEA with recurrent stenosis;
- prior radiation treatment to the neck; and
- other conditions that were used to determine patients at high risk for CEA in the prior carotid artery stenting trials and studies, such as ARCHER, CABERNET, SAPPHIRE, BEACH, and MAVERIC II.

Symptoms of carotid artery stenosis include carotid transient ischemic attack (distinct focal neurologic dysfunction persisting less than 24 hours), focal cerebral ischemia producing a nondisabling stroke (modified Rankin scale < 3 with symptoms for 24 hours or more), and transient monocular blindness (amaurosis fugax). Patients who have had a disabling stroke (modified Rankin scale > 3) would be excluded from coverage.

The determination that a patient is at high risk for CEA and the patient's symptoms of carotid artery stenosis should be available in the patient medical records prior to performing any procedure.

The degree of carotid artery stenosis should be measured by duplex Doppler ultrasound or carotid artery angiography and recorded in the patient medical records. If the stenosis is measured by ultrasound prior to the procedure, then the degree of stenosis must be confirmed by angiography at the start of the procedure. If the stenosis is determined to be less than 70% by angiography, then CAS should not proceed.
n addition, CMS has determined that CAS with embolic protection is reasonable and necessary only if performed n facilities that have been determined to be competent in performing the evaluation, procedure and follow-up necessary to ensure optimal patient outcomes. Standards to determine competency will include specific physician raining standards, facility support requirements and data collection to evaluate outcomes during a required reevaluation.
CMS has created a list of minimum standards modeled in part on professional society statements on competency. All facilities must at least meet CMS's standards in order to receive coverage for carotid artery stenting for high isk patients.
 Facilities must have necessary imaging equipment, device inventory, staffing, and infrastructure to support a dedicated carotid stent program. Specifically, high-quality X-ray imaging equipment is a critical component of any carotid interventional suite, such as high resolution digital imaging systems with the capability of subtraction, magnification, road mapping, and orthogonal angulation.
 Advanced physiologic monitoring must be available in the interventional suite. This includes real time and archived physiologic, hemodynamic, and cardiac rhythm monitoring equipment, as well as support staff who are capable of interpreting the findings and responding appropriately.
 Emergency management equipment and systems must be readily available in the interventional suite such as resuscitation equipment, a defibrillator, vasoactive and antiarrhythmic drugs, endotracheal intubation capability, and anesthesia support.

- Each institution should have a clearly delineated program for granting carotid stent privileges and for monitoring the quality of the individual interventionalists and the program as a whole. The oversight committee for this program should be empowered to identify the minimum case volume for an operator to maintain privileges, as well as the (risk-adjusted) threshold for complications that the institution will allow before suspending privileges or instituting measures for remediation. Committees are encouraged to apply published standards from national specialty societies recognized by the American Board of Medical Specialties to determine appropriate physician qualifications. Examples of standards and clinical competence guidelines include those published in the December 2004 edition of the American Journal of Neuroradiology, and those published in the August 18, 2004 Journal of the American College of Cardiology.
- To continue to receive Medicare payment for CAS under this decision, the facility or a contractor to the
 facility must collect data on all carotid artery stenting procedures done at that particular facility. This data
 must be analyzed routinely to ensure patient safety, and will also be used in the process of recredentialing the facility. This data must be made available to CMS upon request. The interval for data
 analysis will be determined by the facility but should not be less frequent than every 6 months.

Since there currently is no recognized entity that evaluates CAS facilities, CMS has established a mechanism for evaluating facilities. Facilities must provide written documentation to CMS that the facility meets one of the following:

- 1. The facility was an FDA approved site that enrolled patients in prior CAS IDE trials, such as SAPPHIRE, and ARCHER;
- 2. The facility is an FDA approved site that is participating and enrolling patients in ongoing CAS IDE trials, such as CREST;
- 3. The facility is an FDA approved site for one or more FDA post approval studies; or
- 4. The facility has provided a written affidavit to CMS attesting that the facility has met the minimum facility standards. This should be sent to:

Director, Coverage and Analysis Group 7500 Security Boulevard, Mailstop C1-09-06 Baltimore, MD 21244.

The letter must include the following information: Facility's name and complete address; Facility's Medicare provider number; Point-of-contact for questions with telephone number; Mechanism of data collection of CAS procedures; and, Signature of a senior facility administrative official.

A list of certified facilities will be made available and viewable at http://www.cms.hhs.gov/coverage/carotid-stent-facilities.asp. In addition, CMS will publish a list of approved facilities in the Federal Register. A new affidavit is required every two years to ensure that facilities maintain high standards.

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Decision Memo

TO:

Administrative File: CAG # 00085R Carotid Artery Stenting

FROM:

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SUBJECT: Coverage Decision Memorandum for Carotid Artery Stenting

DATE: March 17, 2005

I. Decision

The Centers for Medicare and Medicaid Services (CMS) has determined that the evidence is adequate to conclude that carotid artery stenting (CAS) with embolic protection is reasonable and necessary for the following:

- 1. Patients who are at high risk for carotid endarterectomy (CEA) and who also have symptomatic carotid artery stenosis \geq 70%. Coverage is limited to procedures performed using FDA approved carotid artery stenting systems and embolic protection devices;
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Patients at high risk for CEA are defined as having significant comorbidities and/or anatomic risk factors (i.e., recurrent stenosis and/or previous radical neck dissection), and would be poor candidates for CEA in the opinion of a surgeon. Significant comorbid conditions include but are not limited to:

- congestive heart failure (CHF) class III/IV;
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- previous CEA with recurrent stenosis;
- prior radiation treatment to the neck; and
- other conditions that were used to determine patients at high risk for CEA in the prior carotid artery stenting trials and studies, such as ARCHER, CABERNET, SAPPHIRE, BEACH, and MAVERIC II.

Symptoms of carotid artery stenosis include carotid transient ischemic attack (distinct focal neurologic dysfunction persisting less than 24 hours), focal cerebral ischemia producing a nondisabling stroke (modified Rankin scale < 3 with symptoms for 24 hours or more), and transient monocular blindness (amaurosis fugax). Patients who have had a disabling stroke (modified Rankin scale > 3) would be excluded from coverage.

The determination that a patient is at high risk for CEA and the patient's symptoms of carotid artery stenosis should be available in the patient medical records prior to performing any procedure.

The degree of carotid artery stenosis should be measured by duplex Doppler ultrasound or carotid artery angiography and recorded in the patient medical records. If the stenosis is measured by ultrasound prior to the procedure, then the degree of stenosis must be confirmed by angiography at the start of the procedure. If the stenosis is determined to be less than 70% by angiography, then CAS should not proceed.
In addition, CMS has determined that CAS with embolic protection is reasonable and necessary only if performed in facilities that have been determined to be competent in performing the evaluation, procedure and follow-up necessary to ensure optimal patient outcomes. Standards to determine competency will include specific physician training standards, facility support requirements and data collection to evaluate outcomes during a required reevaluation.
CMS has created a list of minimum standards modeled in part on professional society statements on competency. All facilities must at least meet CMS's standards in order to receive coverage for carotid artery stenting for high risk patients.
Facilities must have necessary imaging equipment, device inventory, staffing, and infrastructure to support a dedicated carotid stent program. Specifically, high-quality X-ray imaging equipment is a critical component of any carotid interventional suite, such as high resolution digital imaging systems with the capability of subtraction, magnification, road mapping, and orthogonal angulation.
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Emergency management equipment and systems must be readily available in the interventional suite such as resuscitation equipment, a defibrillator, vasoactive and antiarrhythmic drugs, endotracheal intubation capability, and anesthesia support.

Each institution should have a clearly delineated program for granting carotid stent privileges and for monitoring the quality of the individual interventionalists and the program as a whole. The oversight committee for this program should be empowered to identify the minimum case volume for an operator to maintain privileges, as well as the (risk-adjusted) threshold for complications that the institution will allow before suspending privileges or instituting measures for remediation. Committees are encouraged to apply published standards from national specialty societies recognized by the American Board of Medical Specialties to determine appropriate physician qualifications. Examples of standards and clinical competence guidelines include those published in the December 2004 edition of the American Journal of Neuroradiology and those published in the August 18, 2004 Journal of the American College of Cardiology.

To continue to receive Medicare payment for CAS under this decision, the facility or a contractor to the facility must collect data on all carotid artery stenting procedures done at that particular facility. This data must be analyzed routinely to ensure patient safety, and will also be used in the process of recredentialing the facility. This data must be made available to CMS upon request. The interval for data analysis will be determined by the facility but should not be less frequent than every 6 months.

Since there currently is no recognized entity that evaluates CAS facilities, CMS has established a mechanism for evaluating facilities. Facilities must provide written documentation to CMS that the facility meets one of the following:

- 1. The facility was an FDA approved site that enrolled patients in prior CAS IDE trials, such as SAPPHIRE, and ARCHER;
- The facility is an FDA approved site that is participating and enrolling patients in ongoing CAS IDE trials, such as CREST;
- 3. The facility is an FDA approved site for one or more FDA post approval studies; or
- 4. The facility has provided a written affidavit to CMS attesting that the facility has met the minimum facility standards. This should be sent to: Director, Coverage and Analysis Group 7500 Security Boulevard, Mailstop C1-09-06 Baltimore, MD 21244.

The letter must include the following information: Facility's name and complete address; Facility's Medicare provider number; Point-of-contact for questions with telephone number; Mechanism of data collection of CAS procedures; and, Signature of a senior facility administrative official.

A list of certified facilities will be made available and viewable at http://www.cms.hhs.gov/coverage/carotid-stent-facilities.asp. In addition, CMS will publish a list of approved facilities in the Federal Register. A new affidavit is required every two years to ensure that facilities maintain high standards.

All other Medicare policies on PTA of the carotid artery apply. $\frac{6}{}$
II. Background
Each year about 700,000 people in the United States experience a new or recurrent stroke. About 500,000 of these are first attacks and 200,000 are recurrent attacks. The term stroke refers to a "group of cerebrovascular disorders in which part of the brain is transiently or permanently affected by ischemia or hemorrhage, or in which one or more blood vessels of the brain are primarily affected by a pathologic process, or both." There are three main categories of strokes: cerebral infarction (greater than 80%), intracerebral hemorrhage, and subarachnoid hemorrhage. Of the cerebral infarctions, "20% to 30% are due to atherothrombosis or thromboembolism from the extracranial or intracranial vessels."
Risk factors for stroke include advanced age, male gender, hypertension, history of stroke or TIA (transient ischemic attack), atrial fibrillation, valvular heart disease, diabetes mellitus, carotid artery stenosis, hypercoagulable conditions, and cigarette smoking. Hypertension is "the single most important risk factor for both ischemic and hemorrhage stroke." 10
Awareness of stroke warning signs is important since "the inability of patients and bystanders to recognize stroke symptoms and to quickly access the emergency medical system are the largest barriers to effective acute stroke therapy." Stroke warning signs include:

sudden numbness or weakness of the face, arm or leg, especially on one side of the body;

sudden confusion, trouble speaking or understanding speech; sudden trouble seeing in one or both eyes;

sudden severe headache with no known cause. 12,13

sudden trouble walking, dizziness, loss of balance or coordination; and

Prevention of stroke remains important and includes among others, treatment of hypertension and diabetes mellitus; smoking cessation; limiting alcohol intake; control of diet and obesity; antiplatelet drugs or anticoagulants for atrial fibrillation and appropriate acute myocardial infarctions; antiplatelet drugs for symptomatic carotid or vertebrobasilar atherosclerosis; and carotid endarterectomy (CEA) for specifically defined populations of patients with symptomatic carotid artery stenosis. 14,15,16 CEA is a surgical procedure used to prevent stroke in which the surgeon removes fatty deposits or ulcerated and stenotic plaques from the carotid arteries, the two main arteries in the neck supplying blood to the brain. Although carotid artery stenosis is an important risk factor, it was estimated that "approximately 20% and 45% of strokes in the territory of symptomatic and asymptomatic carotid arteries with 70% to 99% stenosis, respectively, are unrelated to carotid stenosis." In these patients, optimal medical therapy would be most important since CEA does not reduce lacunar and cardio embolic strokes.

Carotid artery stenting (CAS) is performed with a catheter, usually inserted through the femoral artery, and threaded up to the carotid artery beyond the area of narrowing. A distal embolic protection device or filter is usually placed first to catch emboli or debris that may dislodge during the procedure. A self-expandable or balloon-expandable, metal mesh stent is then placed to widen the stenosis and the protection device is removed.

III. History of Medicare Coverage

On June 18, 2004, CMS began a national coverage determination process for carotid artery stenting (CAS) with distal embolic protection for patients at high risk for CEA. Previously, Medicare covered PTA (percutaneous transluminal angioplasty) of the carotid artery concurrent with stent placement in accordance with the Food and Drug Administration (FDA) approved protocols governing Category B Investigational Device Exemption (IDE) clinical trials and in FDA required post approval studies. Effective July 1, 2001, PTA of the carotid artery, when provided solely for the purpose of carotid artery dilation concurrent with carotid stent placement, is considered to be a reasonable and necessary service only when provided in the context of such a clinical trial, and therefore is considered a covered service for the purposes of these trials. Effective October 12, 2004, Medicare covered PTA of the carotid artery concurrent with the placement of an FDA-approved carotid stent for an FDA-approved indication when furnished in accordance with FDA-approved protocols governing post-approval studies. 18

Reconsideration

Cordis requested that CMS reconsider our position on carotid stenting and that we modify current language in the PTA coverage decision to allow for coverage of carotid stenting outside of Category B IDE trials. A timeline of the background and recent developments and activities is listed below.

Discussion of Related CIMs

Medicare's NCD for PTA concurrent with carotid stenting can be found in CIM 50-32 (NCD Manual 20.7). Medicare's NCD for PTA concurrent with carotid stenting in FDA Post Approval Studies can also be found at CIM 50-32 (NCD Manual 20.7)

Benefit Category Determination

For an item or service to be covered by the Medicare program, it must meet one of the statutorily defined benefit categories outlined in the Social Security Act. PTA concurrent with carotid stent placement falls under the benefit category set forth in section $\S1861(b)(3)$ (inpatient hospital services), part A benefit under $\S1812(a)(1)$ and $\S1861(s)(1)$ (physician services), a part B benefit.

IV. Timeline of Recent Activities

January 6, 2004	Cordis, a subdivision of Johnson & Johnson, submitted a letter requesting that CMS consider expanding coverage for carotid stents.
February 3, 2004	CMS received a letter of support for the potential expansion of coverage for carotid stents signed by various medical, surgical, and radiological specialty societies.
March 19, 2004	On this date a meeting was held at CMS with Medtronic to discuss the MAVERIC II trial and their carotid stenting technologies.
April 22, 2004	CMS met with Guidant Corporation to discuss the ARCHER 12- month data and their carotid stenting technologies.
May 12, 2004	A meeting was held with Cordis to go over physician training and credentialing programs, as well as facility experience.
May 27, 2004	A meeting was held with Guidant to go over a proposed physician training program and facility experience requirements.
June 18, 2004	CMS opened the NCD process based on Cordis' request. Tracking sheet posted. Public comment period began.
July 1, 2004	CMS met with the Society of Interventional Radiology to go over appropriate patient selection criteria, credentialing and training.
July 12, 2004	A meeting was held with the Society for Vascular Medicine and Biology and the Society for Cardiovascular Angiography and Interventions to go over appropriate patient selection criteria, credentialing and training.
July 18, 2004	The Carotid Stenting NCA tracking sheet public comment period ended. We received 140 pages of public comments which are posted on the tracking sheet at http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=128
July 21, 2004	A meeting was held with the American Society of Interventional Therapeutic Neuroradiology to go over appropriate patient selection criteria, credentialing and training.
August 10, 2004	CMS met with Abbott Laboratories to go over new clinical data for their new carotid stenting system.
August 17, 2004	A town hall meeting was held at CMS central office in Baltimore to discuss training for physicians and hospital staff for carotid stent placement. Attendees included members from medical device industry, FDA and various physician professional societies.
September 1, 2004	CMS posted its draft Decision Memorandum on Carotid Artery Stenting in Post Approval Studies, announcing expanded coverage in these trials.
September 9, 2004	CMS met with Boston Scientific to go over their proposed physician training programs.
October 12, 2004	CMS posted the final Decision Memorandum on Carotid Artery Stenting in Post Approval Studies along with public comments.

December 17, 2004 CMS posted the proposed Decision Memorandum on Carotid Artery Stenting and opened

the initial 30 day comment period.

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Februa	ary 4, 2005	CMS announced that it is still interested in comments on the sustainability of a national evaluation process to ensure qua	
V. FD/	A Status		
FDA S	ection		
decision device proced asymp	on voted to rece of carotid stess should not in lure for those patien mending appro	an FDA Advisory Panel met to review Cordis' carotid stent PMA ecommend approval. During that meeting several public completenting in asymptomatic individuals, and even suggested that include asymptomatic patients, due to minimal evidence on the patients. During the panel's deliberations, the appropriateness and population continued to raise concerns. The panel members roval consistently cited the lack of compelling evidence demonstrated patients.	menters raised concerns over the labeled indication for the e degree of benefit of the s of using the device in the s that voted against
Systen	n under a PMA	4, FDA granted Guidant Corporation clearance to market their A for the indicated treatment of patients at high risk for advers o require carotid revascularization and meet the criteria outline	se events from carotid
1.	ultrasound or	n neurological symptoms and > 50% stenosis of the common or angiogram OR patients without neurological symptoms and arotid artery by ultrasound or angiogram, AND	
2.	Patients must lesion.	st have a reference vessel diameter within the range of 4.0 mn	n and 9.0 mm at the target

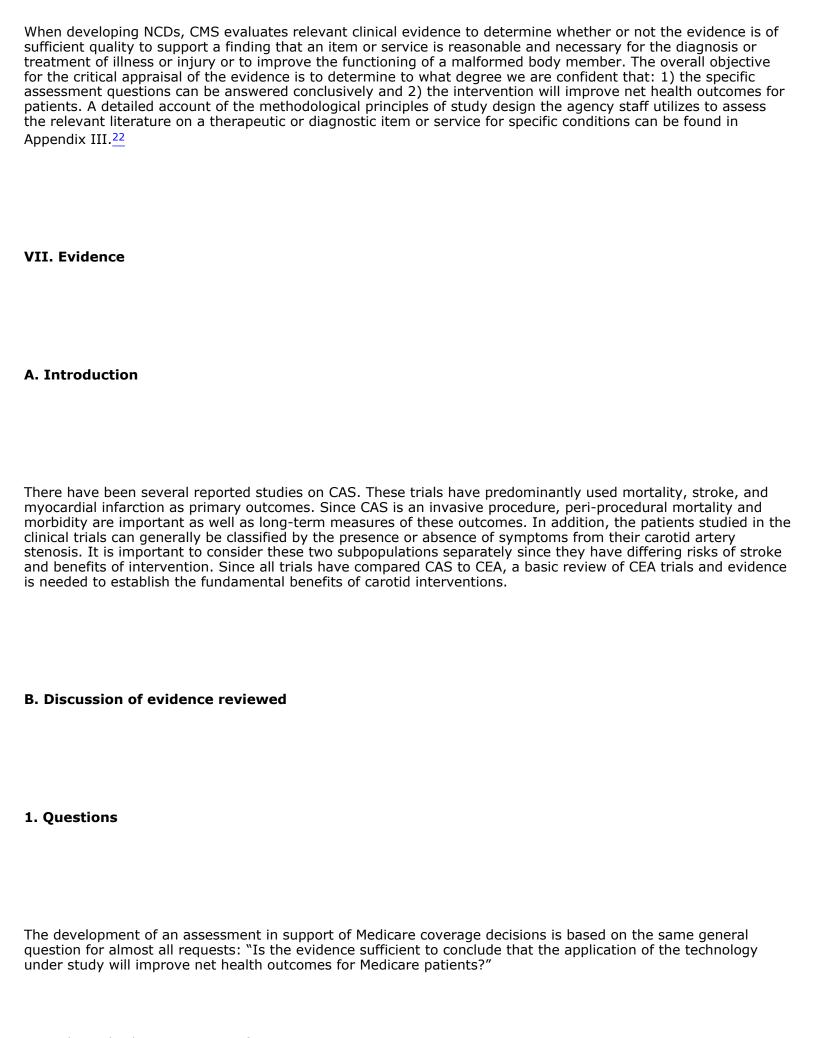
Currently, Guidant is the only manufacturer with FDA approval under a PMA (post market approval) to market their carotid stent system, although it will be possible for other companies to receive clearance for their carotid stenting devices under a PMA as well. FDA has not approved carotid artery stenting systems for use in low to moderate risk patients. Use of these devices for that indication would represent off-label use.²⁰

Both CMS and the FDA review scientific evidence, and may review the same evidence, to make purchasing and regulatory decisions. However, CMS and its contractors make coverage determinations and the FDA conducts premarket review of products under different statutory standards and different delegated authority (67 FR 66755, November 1, 2002). Whereas the FDA must determine that a product is safe and effective as a condition of approval, CMS must determine that the product is reasonable and necessary as a condition of coverage under section 1862(a)(1)(A) of the Act. CMS adopts FDA determinations of safety and effectiveness, and CMS evaluates whether or not the product is reasonable and necessary for the Medicare population. Although an FDA-regulated product must receive FDA approval or clearance (unless exempt from the FDA premarket review process) for at least one indication to be eligible for Medicare coverage, except for Category B devices under an IDE clinical trial (see 60 FR 48417, September 19, 1995), FDA approval/clearance alone does not generally entitle that device to coverage. Amongst other things, CMS evaluates whether or not the intervention improves net health outcomes in the Medicare population at least as well as established treatments. Thus, FDA PMA approval alone is not sufficient for making a determination concerning Medicare coverage.

The same applies to FDA Premarket notification (510(k)) clearance. As we stated in 66 FR 58788, 58797 (November 23, 2001), "[t]he criteria the FDA uses in making determinations related to substantial equivalency under section 510(k) of the Food, Drug, and Cosmetic Act is significantly different from the scientific evidence considered in making a determination that a device is "reasonable and necessary" by Medicare. FDA does not necessarily require clinical data or outcomes studies for a determination of substantial equivalency for clearance of a device under section 510(k) of the Food, Drug, and Cosmetic Act. Medicare NCDs consider medical benefit and clinical utility of an item or service in determining whether the item or service is considered reasonable and necessary under the Medicare program. Thus, a Premarket notification cleared under section 510(k) of FDA is not sufficient for determination of Medicare coverage."

In Section VII of this decision memorandum, CMS further discusses the application of these differences in the analysis of the evidence.

VI. General Methodological Principles



The formulation of specific questions for the assessment recognizes that the effect of an intervention can depsubstantially on how it is delivered, to whom it is applied, the alternatives with which it is being compared an the delivery setting. In this reconsideration, CMS sought to address the following questions:	
 Is the evidence sufficient to conclude that carotid artery stenting improves health outcomes for patier with symptomatic carotid artery stenosis and who are at high risk for CEA? a. What degree of stenosis should be treated? Is the evidence sufficient to conclude that carotid artery stenting improves health outcomes for patier with asymptomatic carotid artery stenosis > 80% and who are at high risk for CEA? 	
2. External technology assessments	
In February 2005, after the close of the public comment period, the Blue Cross Blue Shield Association Technology Evaluation Center (TEC) published an evidence-based technology assessment on carotid artery stenting with distal embolic protection (DEP).23	
Pertinent Excerpts from the Executive Summary:	
"Based on the available evidence, the Blue Cross and Blue Shield Medical Advisory Panel made the following judgments about whether carotid artery angioplasty and stenting with or without distal embolic protection m the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria to reduce stroke risk symptomatic or asymptomatic carotid stenosis."	eets fron
1. The technology must have final approval from the appropriate governmental regulatory bodies	-

"CAS with or without DEP is a procedure and thus does not require U.S. Food and Drug Administration (FDA) approval. However, the devices used for CAS and for DEP require FDA approval. As of this writing, one manufacturer's stents (ACCULINK™ and RX ACCULINK™; Guidant Corp.) and cerebral protection filters (ACCUNET™ and RX ACCUNET™; Guidant Corp.) are FDA approved and indicated specifically for use in carotid arteries. The Guidant devices were approved on August 30, 2004, based on uncontrolled, single-arm trials and comparison to historical controls. The approved stents and filters differ in the deployment method used once they reach the target lesion, with the RX devices designed for more rapid stent and filter expansion.

The FDA has mandated postmarketing studies for these devices, including longer follow-up for patients already reported to the FDA and additional registry studies primarily to compare outcomes as a function of clinician training and facility experience. The Guidant devices are indicated for combined use of a stent and DEP device to reduce stroke risk in patients at high risk for perisurgical complications from CEA and who are symptomatic with \geq 50% stenosis or asymptomatic with \geq 80% stenosis. Criteria to define those at high risk for CEA are specified in Guidant's Information for Prescribers. CAS with these devices for patients outside these indications is an unlabeled use.

The Cordis Corporation received an "approvable" letter from the FDA for its stent and DEP device (Precise™ stent and AngioGuard™ embolic protection device) after an FDA Advisory Panel voted 6-5 in favor of recommending approval at an April 21, 2004, meeting. However, the FDA has not granted final approval for these devices as of this writing. Apparently, the FDA will also require continued follow-up and additional postmarketing studies for the Cordis devices, similar to those mandated for the Guidant devices.

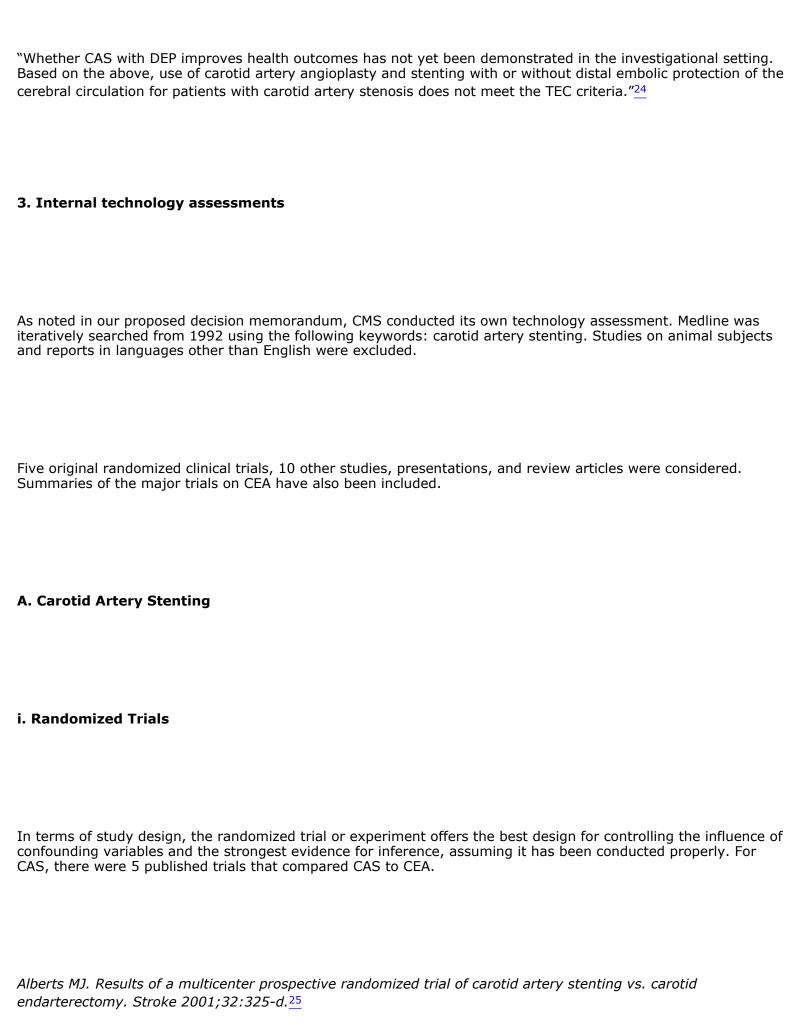
Pivotal trials of several other manufacturers' stents and DEP devices are complete or nearly so, but have not been reviewed by the FDA as of this writing. Among these are:

- ev3 Inc.'s Protege® Tapered Stent and SpideRX™ protection device, which have been approved in Europe; a manufacturer's press release estimates the U.S. pivotal trial should be completed in the third quarter of 2004 and an application for FDA approval will be submitted subsequently.
- Medtronic Inc.'s Exponent™ carotid stent and Interceptor® PLUS carotid filter system, which also are approved in Europe; pivotal trial data were presented at the Transcatheter Cardiovascular Therapeutics (TCT) meeting in Washington, DC on September 29, 2004, but it is uncertain when an application for approval will be submitted to FDA.
- The NexStent™ (EndoTex Interventional Systems), used in conjunction with Boston Scientific's FilterWire EX™ or EZ™ Embolic Protection Systems; 30-day results with these devices were also reported at the TCT meeting on September 29th, but information is as-yet unavailable on longer-term outcomes and on anticipated date(s) for submitting an application to FDA for NexStent approval. The Boston Scientific DEP devices were cleared for marketing in the U.S., but indicated for use in saphenous vein grafts."

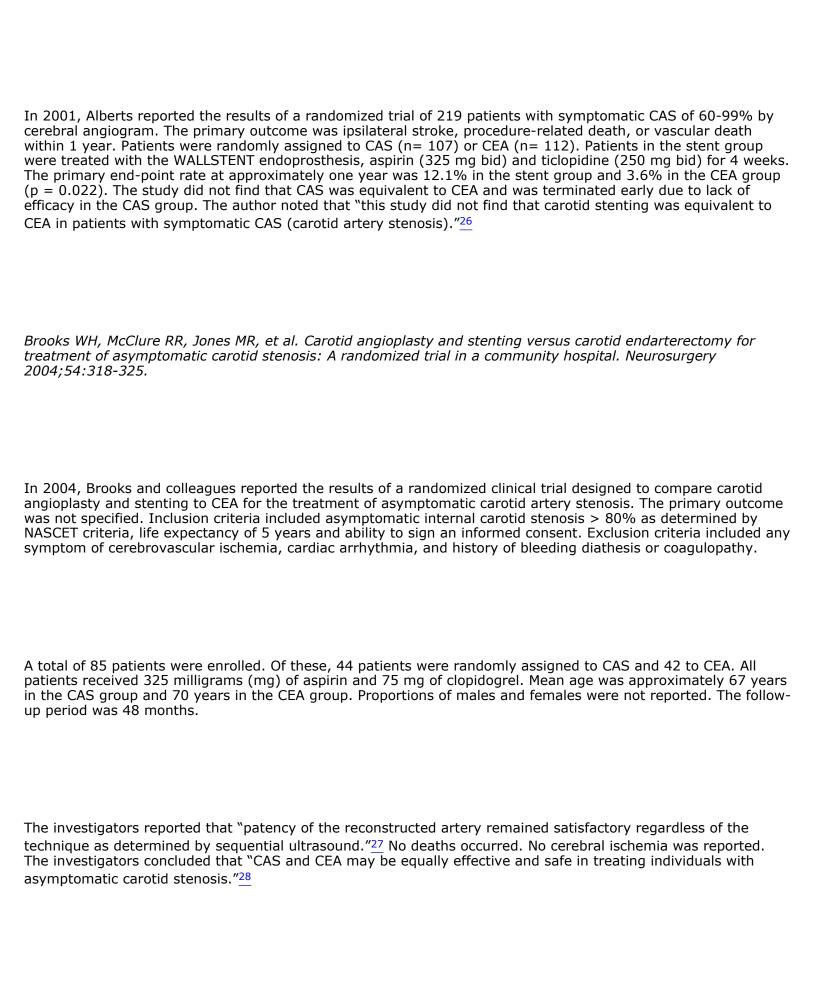
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

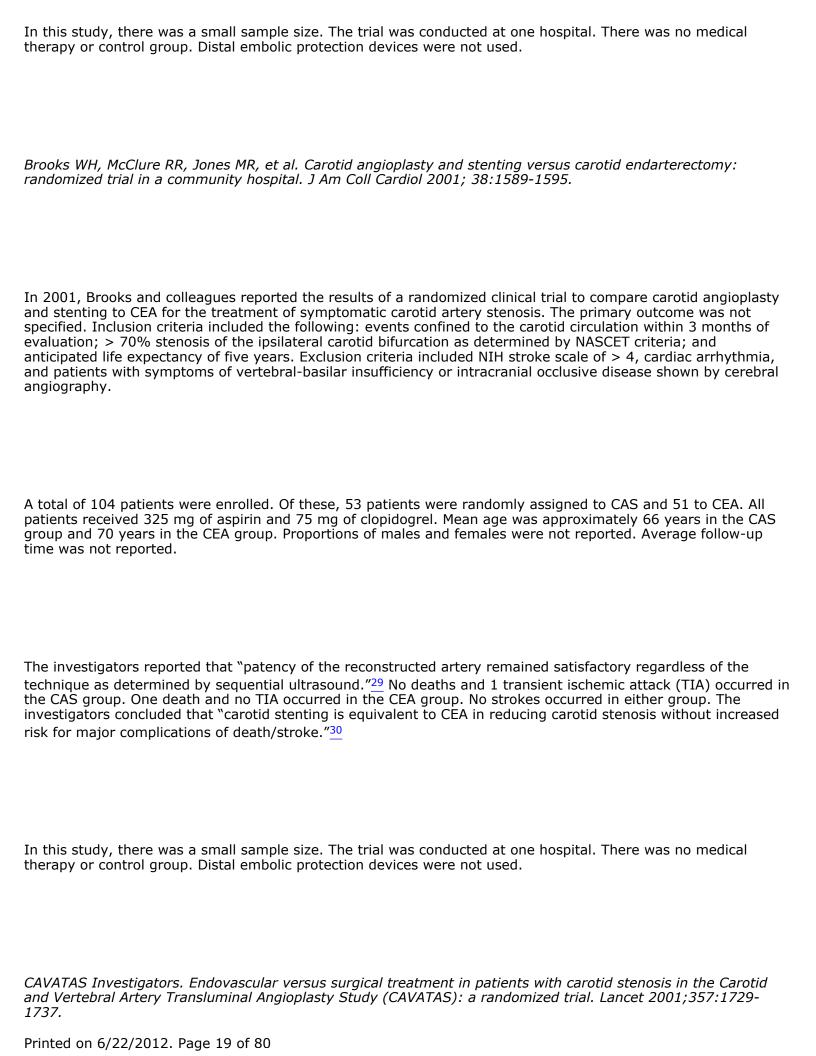
"The only trial reported thus far that directly compares outcomes of CEA plus MM versus outcomes of CAS with DEP plus MM (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; SAPPHIRE) included no patients with symptomatic (Indication 1) or asymptomatic (Indication 2) carotid stenosis at average risk for perisurgical complications from CEA. Because it included so few patients with symptomatic stenosis at high risk for perisurgical complications from CEA (Indication 3; n=96), reported differences in 30-day and 1-year outcomes between arms had wide confidence intervals and were not statistically significant. For those with asymptomatic stenosis at high risk for perisurgical complications from CEA (Indication 4), differences in 30-day outcomes also had wide confidence intervals and were not statistically significant. Although differences in 1-year outcomes for this last indication favored CAS with DEP and were statistically significant, the adequacy of 1 year follow-up duration is questionable, since durability of benefits from CAS with DEP is unknown and since the time to benefit relative to medical management is long when surgical risks are high.
The need for adequate follow-up is underscored by data in the FDA Reviewers' Memo on a subset of SAPPHIRE patients followed for 2 years after treatment showing more frequent restenosis among those randomized to CAS + DEP (38.7%) than among those randomized to CEA (26.6%). Also, early study closure with insufficient patients compromised the statistical test for non-inferiority of treatments. Variance in differential complication rates for the two treatments across sites may have influenced results, since 5 of 34 sites contributed 64% of randomized patients and data were unavailable for comparison. Additionally, direct comparative evidence is lacking for optimal medical management alone as an alternative to adding CAS with DEP or CEA for high surgical risk patients. Thus, available evidence does not permit conclusions on outcomes of CAS with DEP for any indication considered in this Assessment."
3. The technology must improve the net health outcome.
"Whether CAS with DEP improves net health outcome cannot be determined since available evidence is insufficient to permit conclusions."
4. The technology must be as beneficial as any established alternatives.
"Whether CAS with DEP is as beneficial as either CEA or optimal medical management for high surgical risk patients cannot be determined since available evidence is insufficient to permit conclusions."

5. The improvement must be attainable outside the investigational settings.



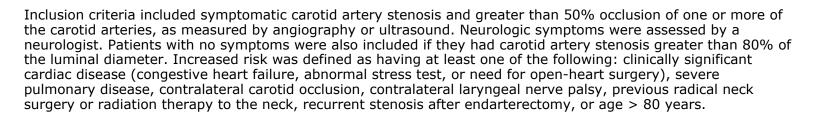
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CAVATAS was a prospective, randomized clinical trial designed to test the hypothesis that endovascular treatment (balloon dilation or use of a stent) of carotid stenosis would have the same major complication rates and less minor morbidity than CEA. The primary outcome was death or any stroke. Inclusion criteria included stenosis of the common carotid artery, carotid bifurcation, or internal carotid artery that investigators believed needed treatment and was suitable for both carotid endarterectomy and endovascular treatment. Investigators used their own protocol to determine the need for treatment. Exclusion criteria included medical or surgical risk factors such as recent myocardial infarction, poorly controlled hypertension or diabetes mellitus, renal disease, respiratory failure, inaccessible carotid stenosis, or severe cervical spondylosis.
A total of 505 patients were enrolled. Of these, 251 patients were randomly assigned to endovascular treatment and 253 to surgical treatment. One patient was excluded due to carotid occlusion. Mean age was 67 years. Men comprised about 70% of the study population. About 97% of the patients had cerebrovascular symptoms within 6 months before randomization. An independent neurologist evaluated patients. Stents suitable for use in the carotid arteries were developed during the course of the study and used in 55 patients.
There were 25 events (7 deaths and 18 strokes; 10% event rate) in the endovascular group compared to 25 events (4 deaths and 21 strokes; 10% event rate) in the surgical group within 30 days. The investigators concluded that "endovascular treatment had similar major risks and effectiveness at prevention of stroke during 3 years compared with carotid surgery." 31
In this study, there was no medical therapy or control group. There was no uniform protocol for inclusion. Stents were used in 55 patients. All patients received antiplatelet therapy. Distal embolic protection devices were not used.
Yadav JS, Wholey MH, Kuntz KE, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 2004;351:1493-1501.
The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial was a prospective, randomized trial designed to test the hypothesis that CAS was not inferior to CEA. The primary outcome was cumulative incidence of death, stroke, or myocardial infarction within 30 days after the procedure or death or ipsilateral stroke between 31 days and 1 year. The trial was designed as a non-inferiority trial.

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Exclusion criteria included ischemic stroke within previous 48 hours, presence of intraluminal thrombus, total occlusion of target vessel, vascular disease precluding use of catheter-based techniques, intracranial aneurysm >9 mm in diameter, need for more than 2 stents, history of bleeding disorder, percutaneous or surgical intervention planned within next 30 days, life expectancy < 1 year, and ostial lesion of common carotid artery or brachiocephalic artery.

A total of 747 patients were enrolled in the trial. Of these, 334 patients were randomly assigned to either carotid artery stenting with embolic protection (n=167) or carotid endarterectomy (n=167). Patients who received CAS were also treated with 75 mg of clopidogrel per day for 2-4 weeks. Mean age was 73 years. About 20% of patients were > 80 years. Men comprised 67% of the study population. Approximately 30% of patients in the CAS group had symptomatic stenosis. Approximately 28% of patients in the CEA group had symptomatic stenosis. Degree of stenosis was not reported.

The primary endpoint occurred in 20 patients (12.2%) in the stenting group compared to 32 patients (20.1%) in the endarterectomy group (p=0.004 for noninferiority). The investigators reported that "among patients with severe carotid-artery stenosis and coexisting conditions, carotid stenting with the use of an emboli-protection device is not inferior to carotid endarterectomy."³²

In this trial, there was 1:1 randomization to the treatment groups. A large proportion (55%) of the patients who were enrolled in the study were not randomly assigned to treatment. There was no medical therapy or control group. Since only patients who underwent CAS received clopidogrel therapy, it is a potential confounder and should be considered a co-treatment. Average follow-up time was not reported. Symptoms of carotid artery stenosis were not specifically reported. The trial was ended early due to decreased enrollment.

ii. Ongoing Trials on CAS Several trials comparing CAS to CEA are ongoing and summarized below: **CREST -** Carotid Revascularization Endarterectomy versus Stent Trial³³ Study Design: Prospective, randomized, clinical trial on lower risk patients. Inclusion Criteria: Patients who have experienced a TIA, amaurosis fugax (AF), or non-disabling stroke within the past 180 days, and who have an ipsilateral carotid stenosis > 50% by angiography or 70% by ultrasound will be Exclusion Criteria: Patients who have comorbid conditions that interfere with the evaluation of endpoints, that are known to interfere with the completion of CEA or CAS, or that affect the likelihood of survival for the 4-year study period, will be excluded. Patient Involvement: Eliqible patients will be randomized to undergo either CAS or CEA. All will receive aspirin, antiplatelet therapy, treatment for hypertension, and management of other stroke risk factors. Follow-up will last four years. Primary Outcome: Death, stroke, or myocardial infarction at 30 days postoperatively; ipsilateral stroke at 60 days post-operatively.

EVA-3S Endarterectomy Versus Angioplasty in patients with Severe Symptomatic carotid Stenosis³⁴

Study Design: Prospective Randomized Open Blinded End-point (PROBE) Study.

Inclusion Criteria: Patients presenting within 4 months of ischemic cerebral or retinal stroke will be eligible. Patient Involvement: Eligible patients will be randomized to undergo either carotid endarterectomy or angioplasty with stenting. Angioplasty patients will receive either ticlopidine or clopidogrel for 1 month after the procedure. Patients in both groups will receive follow-up visits at 1 month, 6 months, and every 6 months thereafter for 2 - 4 years. Duplex scans will be performed at the time of the procedure, and every 6 months for the duration of the study. Patients in the angioplasty group will undergo blood draws at 15 days and 1 month, and a simple cervical radiogram at 2 years after the procedure.

Primary Outcome: All mortality and all recurrence of stroke within 30 days, all ipsilateral stroke within 2 - 4 years.

Study Design: Open, prospective, randomized, multicenter trial.

Inclusion Criteria: Patients older than 40 years with symptomatic severe (\geq 70%), whose carotid stenoses are suitable for primary stenting and surgical endarterectomy, who are able to begin treatment as soon as possible after randomization, and who have no indication or contraindication to either treatment will be eligible. *Exclusion Criteria*: Patients who have had a major stroke with minimal recovery of function in the territory of the artery in question, who are unsuitable for stenting due to tortuous anatomy proximal or distal to the stenosis, the presence of a visible thrombus, proximal carotid artery stenotic disease, pseudo-occlusion, high stenosis, or rigid neck, who are medically unfit for surgery, or who have a life expectancy < 2 years will be excluded. *Primary Outcome*: Incidence of mortality and debilitating (modified Rankin score (MRS) < 3 for 30 days after onset) stroke.

SPACE - Stent-protected Percutaneous Angioplasty of the Carotid vs. Endarterectomy 36

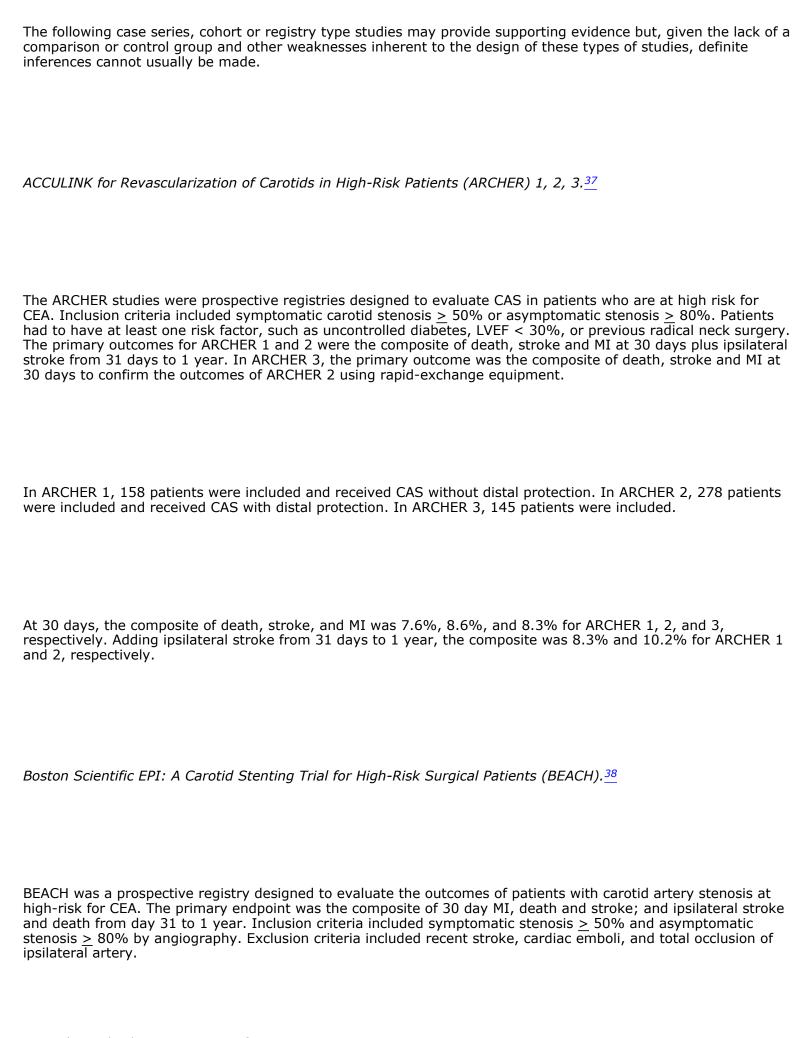
Study Design: Prospective, randomized, independently-controlled, multicenter trial.

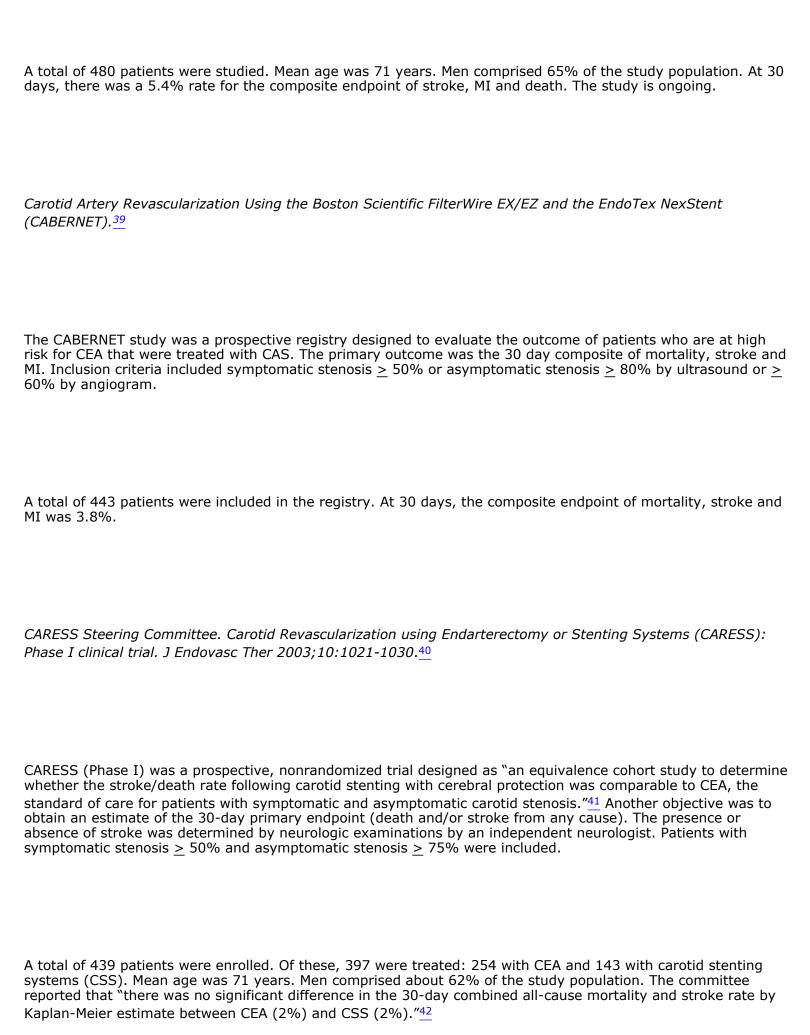
Inclusion Criteria: Patients with severe carotid stenosis (\geq 70% by Duplex sonography, \geq 50% by NASCET criteria, or \geq 70% by ECST criteria) who have experienced amaurosis fugax, TIA, prolonged reversible ischemic neurological deficit (PRIND), or other mild stroke within 180 days of randomization, amaurosis fugax, or non-disabling stroke (mod. Rankin \leq 3) occurring within 180 days will be eligible.

Exclusion Criteria: Pregnant females, and persons with a history of intracranial bleeding within 90 days of randomization, who have a confirmed arteriovenous malformation or aneurysm, who have a serious comorbid illness limiting life expectancy < 2 years, who have an uncontrolled coagulopathy, who have any contraindication for heparin, ASA, clopidogrel, or contrast media, who have stenosis or dissection of the common and/or internal carotid arteries, who have stenosis following surgical or endovascular pretreatment, whose stenoses result from radiation therapy, fibromuscular dysplasia, or endovascular thrombosis, who have tandem stenoses (if the distal stenosis is the more severe), who have other planned surgical interventions, or who have any comorbid condition that, in the opinion of the investigator, would interfere with the study, will be excluded.

Primary Outcome: 30-day incidence of ipsilateral cerebrovascular events (cerebral infarction and/or hemorrhage with symptoms lasting for more than 24 hours); 30-day mortality.

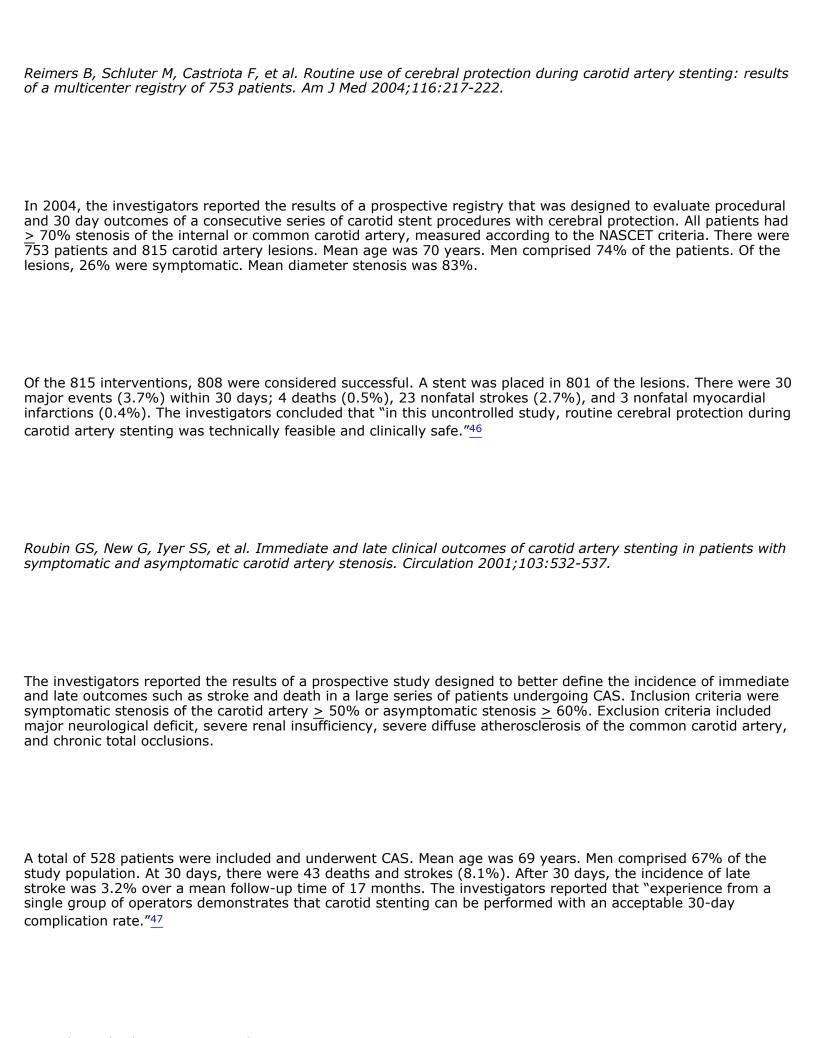
iii. Other Published or Presented Studies on CAS

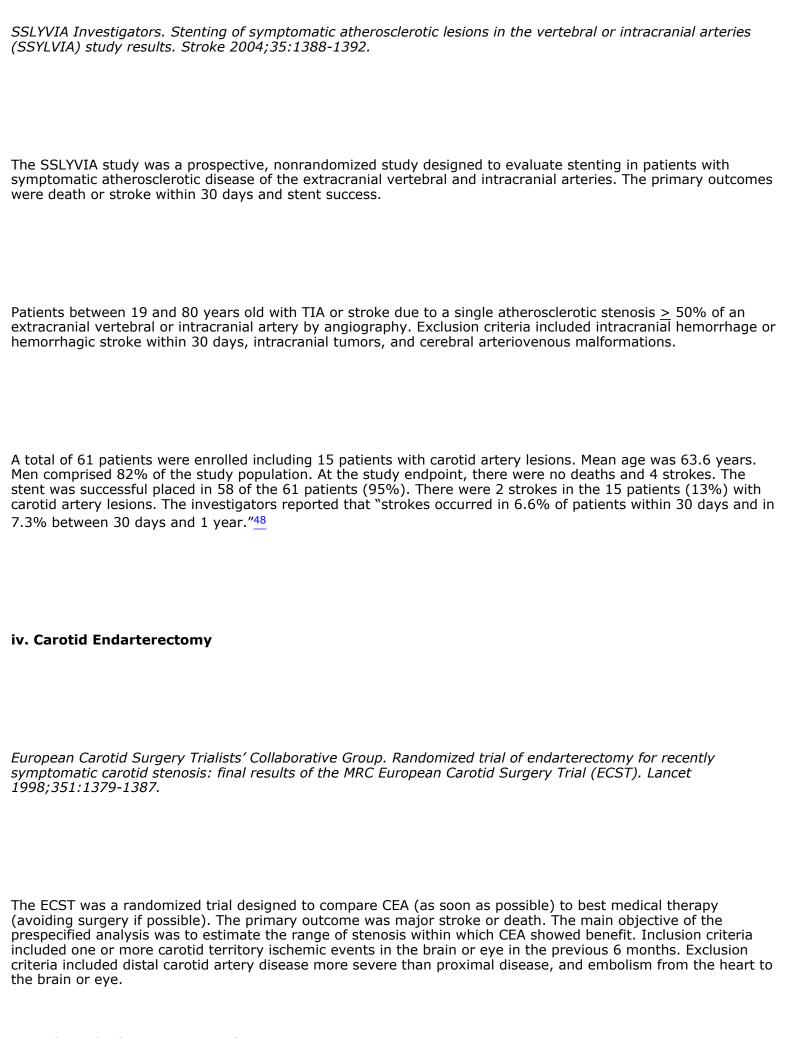




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Cordis Smart Self-Expandable Stent in Carotid Artery Disease (CASCADE).43
The CASCADE study was a prospective registry of 121 patients. Inclusion criteria included stenosis between the origin of the common carotid artery and extracranial segment of the internal carotid artery and either symptomatic stenosis > 70% or asymptomatic stenosis > 85% by ultrasound or angiography. The primary outcome was ipsilateral stroke or procedural related death within 30 days of stent implantation. Overall 7.4% of the study population had an ipsilateral stroke. There were no deaths at 30 days. For patients who had CAS with embolic protection, 3.2% had an ipsilateral stroke compared to 8.9% for patients without embolic protection.
Cremonesi A, Manetti R, Setacci F, Setacci C, Castriota F. Protected carotid stenting: clinical advantages and complications of embolic protection devices in 442 consecutive patients. Stroke 2003;34:1936-1943.
In 2003, the investigators reported the results of a study to evaluate in-hospital and 30-day adverse events for patients undergoing CAS with embolic protection. A total of 442 consecutive patients with symptomatic carotid artery stenosis > 75% were treated. The authors stated: "The percutaneous procedure was successful in 440 of 442 patients (99.5%). No periprocedural death occurred with any embolic protection device. All in-hospital stroke/death and 30-day ipsilateral stroke/death rate was 1.1%. The overall complication rate was 3.4%. Major adverse events included 1 major stroke (0.2%), 4 intracranial hemorrhages (0.9%), 1 carotid artery wall fissuration (0.2%), and 1 diffuse cardioembolism (0.2%)."44
Medtronic AVE Self-Expanding Carotid Stent System in the Treatment of Carotid Stenosis II (MAVERIC II). 45
The MAVERIC II study was a prospective registry designed to evaluate the safety and efficacy of CAS for patients at high risk for CEA. The primary outcome was a composite of death, ipsilateral stroke and MI at 1 year. The secondary outcome was a composite of death, ipsilateral stroke and MI at 30 days. A total of 339 patients were included in the registry. The primary outcome was not presented. The secondary outcome at 30 days was 5.3%.

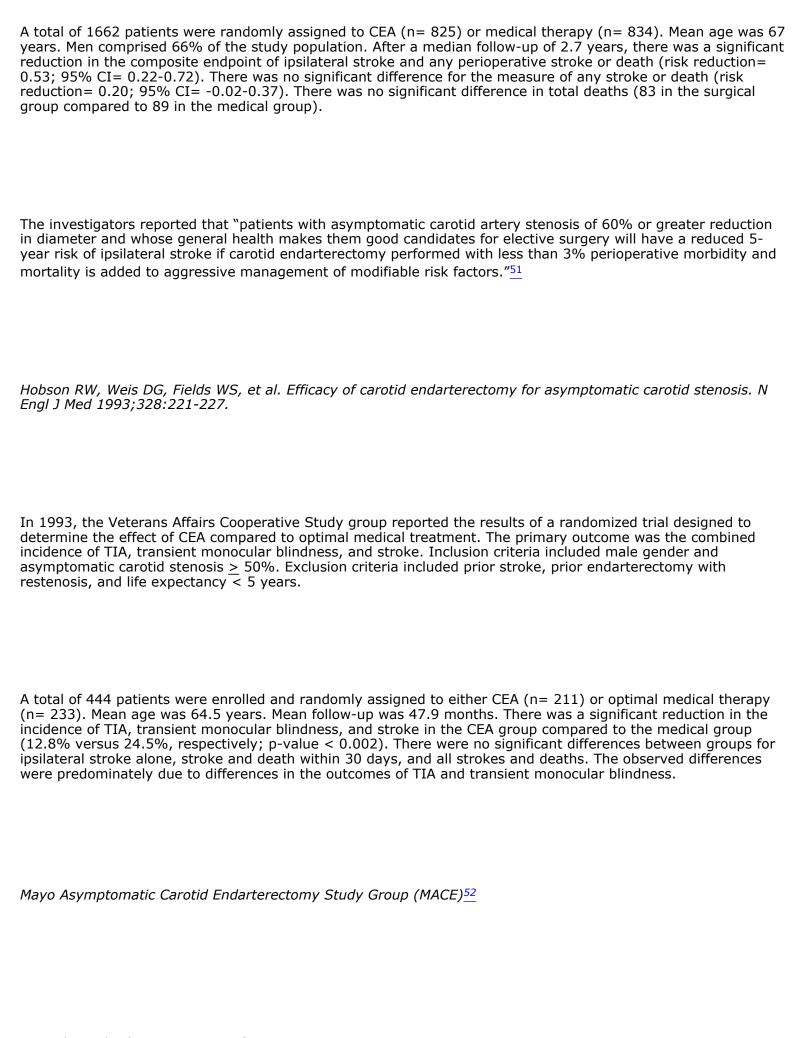


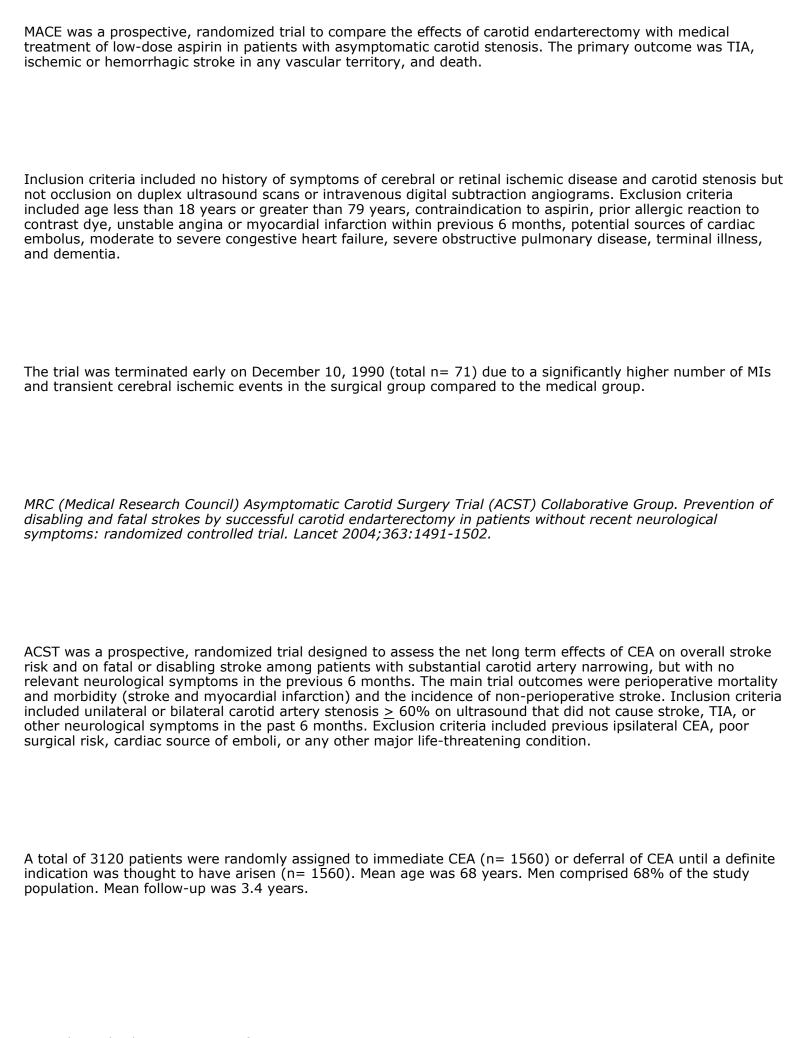


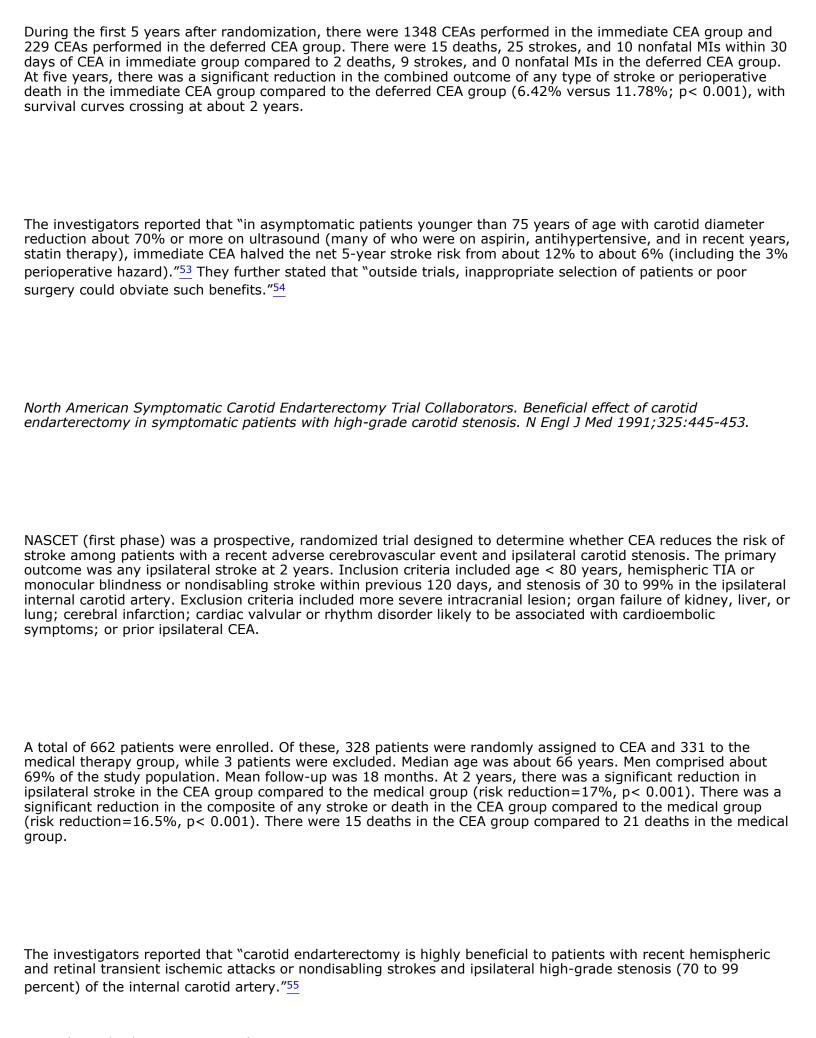


could seriously complicate surgery; or a condition that could prevent continuing participation or was likely to

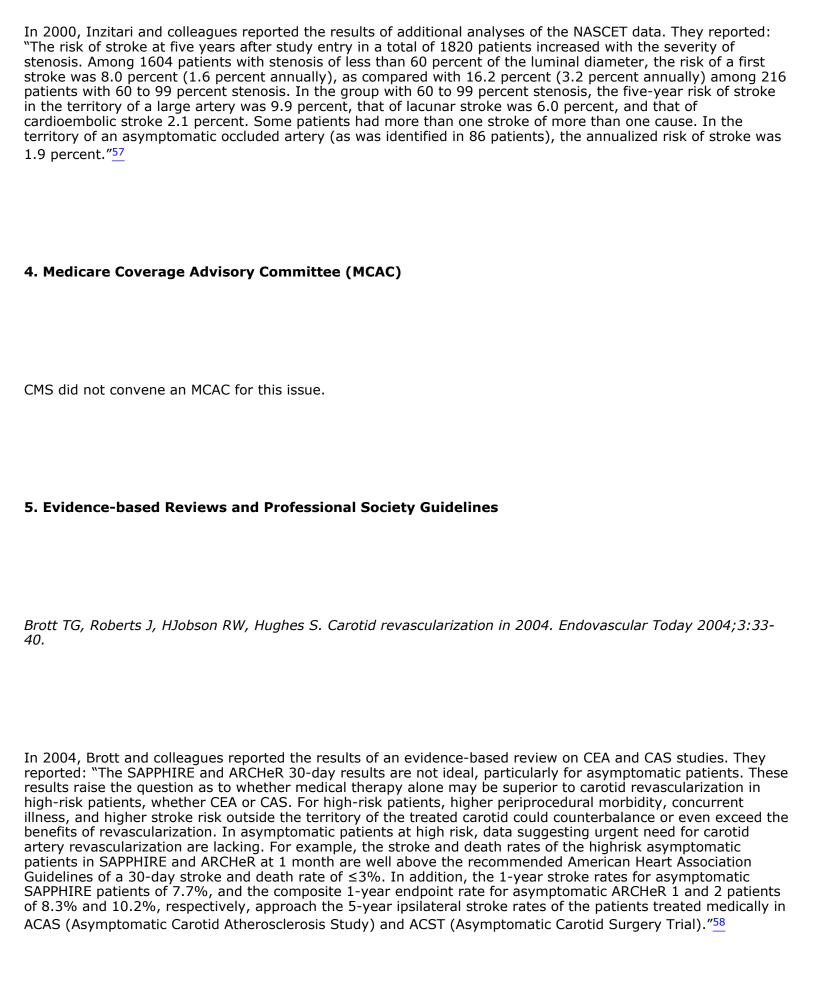
produce disability or death within 5 years.

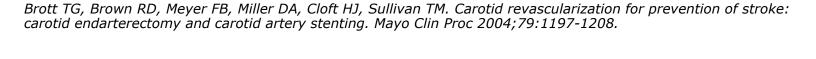












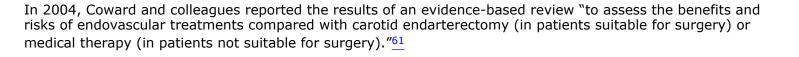
In 2004, Brott and colleagues reported the results of an evidence-based review on CEA and CAS studies. They reported: "The SAPPHIRE and ARCHER 30-day results are not ideal and raise the question of whether medical therapy alone may be superior to carotid revascularization (CEA or CAS) in high-risk patients. Except for NASCET (North American Symptomatic Carotid Endarterectomy Trial), the NNT (number needed to treat) for symptomatic and asymptomatic patients in all the large RCTs (Tables 1 and 2) is modest in moderate-risk patients. For high-risk patients, higher periprocedural morbidity, concurrent illness, and higher stroke risk outside the territory of the treated carotid artery could counterbalance or even exceed the benefits of revascularization."59

Connors JJ, Sacks D, Furlan AJ, et al. Training, competency, and credentialing standards for diagnostic cervicocerebral angiography, carotid stenting, and cerebrovascular intervention. Am J Neuroradiol 2004;25:1732-1741.

In 2004, the American Academy of Neurology, the American Association of Neurological Surgeons, the American Society of Interventional and Therapeutic Neuroradiology, the American Society of Neuroradiology, the Congress of Neurological Surgeons, and the Society of Interventional Radiology released a consensus statement that addressed carotid artery stenting. The consensus statement stated the following:⁶⁰

- 1. All collaborating neuroscience societies are of the unanimous opinion that the safety of the patient is paramount.
- 2. Defined formal training and experience in both the cognitive and technical aspects of the neurosciences are essential for the performance and interpretation of diagnostic and therapeutic cervical and cerebrovascular procedures.
- 3. All collaborating neuroscience societies endorse the principles of the several published standards from our various societies for training and quality concerning cervicocerebral angiography and intervention.
- 4. All collaborating neuroscience societies recommend appropriately supervised cervicocerebral angiography training and resultant credentialing with an accumulated total of 100 diagnostic cervicocerebral angiograms before post-graduate training in cervicocerebral interventional procedures, including carotid stenting.
- 5. All collaborating neuroscience societies endorse the principles of training and quality assurance espoused in the multisociety Quality Improvement Guidelines for the Performance of Carotid Angioplasty and Stent Placement, which include a defined training pathway for any qualified practitioner for carotid stent training.
- 6. All collaborating neuroscience societies specifically endorse the principles of the ACGME and the training programs in Endovascular Surgical Neuroradiology, Vascular Neurology and Neuroradiology.

Coward LJ, Featherstone RL, Brown MM. Percutaneous transluminal angioplasty and stenting for carotid artery stenosis. Cochrane Database Syst Rev 2004:CD000515.



Four completed trials were reviewed. The authors reported: "Data from randomized trials comparing endovascular treatment for carotid artery stenosis with carotid endarterectomy suggest that the two treatments have similar early risks of death or stroke and similar long term benefits. However, the substantial heterogeneity renders the overall estimates of effect somewhat unreliable. Furthermore, two trials were stopped early because of safety concerns, so perhaps leading to an over-estimate of the risks of endovascular treatment. On the other hand, endovascular treatment appears to avoid completely the risk of cranial neuropathy. There is also uncertainty about the potential for restenosis to develop and cause recurrent stroke after endovascular treatment. The current evidence does not support a widespread change in clinical practice away from recommending carotid endarterectomy as the treatment of choice for suitable carotid artery stenosis. There is a strong case to continue recruitment in the current randomized trials comparing carotid stenting with endarterectomy."⁶²

Creager MA, Goldstone J, Hirshfeld JW, et al. ACC/ACP/SCAI/SVMB/SVS clinical competence statement on vascular medicine and catheter-based peripheral vascular interventions: A report of the American College of Cardiology/American Heart Association/ American College of Physicians Task Force on Clinical Competence (ACC/ACP/SCAI/SVMB/SVS Writing Committee to develop a clinical competence statement on peripheral vascular disease). JACC 2004;44:941-957.

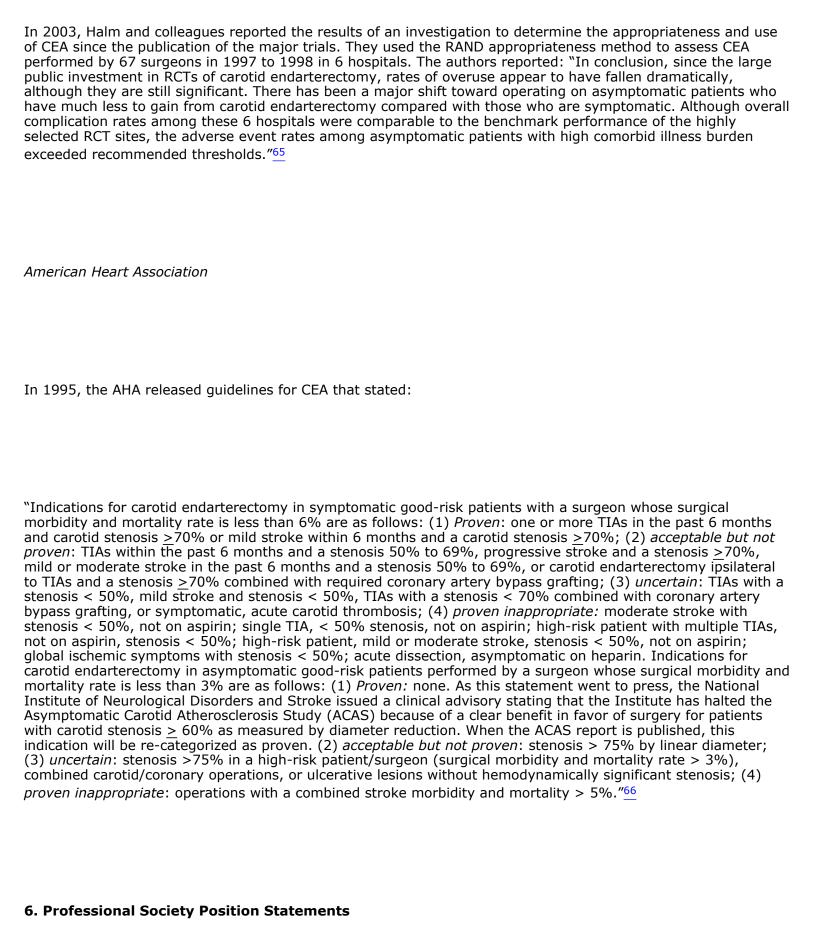
In 2004, the American College of Cardiology (ACC), the American College of Physicians (ACP), the Society for Cardiovascular Angiography and Interventions (SCAI), the Society for Vascular Medicine and Biology (SVMB), and the Society for Vascular Surgery (SVS) released a clinical competence statement that included a section on carotid artery stenting. They reported:

"Obtaining competence in the performance of procedures and interventions in the extracranial cerebral vessels (i.e., carotid and vertebral arteries) is considered a unique category on the following bases: first, although there is crossover in the technical skills from other vascular territories, unique challenges are associated with cannulating the carotid and vertebral arteries and performing interventions in these circulatory beds; and second, there are obvious special issues related to the distribution and target organ of these vessels, which allow for very narrow safety margins. For those performing carotid or vertebral procedures, suggested requirements for achievement of competence include mastery of the cognitive and clinical skills pertaining specifically to this vascular bed and these procedures. This includes, as with other sites, a complete understanding of the anatomical and pathological characteristics unique to this vascular bed and the ability to interpret relevant angiographic images. To achieve competence, a minimum of 30 diagnostic cerebrovascular angiograms, 15 as supervised primary operator, and a minimum of 25 supervised interventions, at least one-half as primary operator, should be performed, with appropriate documentation, follow-up, and outcomes assessment. The recommended number of procedures reflects the consensus of the expert opinion of the committee. It is acknowledged that catheter-based intervention of the extracranial cerebral arteries is an area of competence that is in evolution. Accordingly, these recommendations may be modified in future documents as experience and clinical evidence regarding its safety and efficacy is acquired. Also, as with procedures in other regional vascular venues, it is anticipated that for some physicians to achieve competence, supervising faculty will recommend additional cases beyond the minimum number."63

O'Rourke F, Dean N, Akhtar N, Shuaib A. Current and future concepts in stoke prevention. CMAJ 2004;170:1123-1133.

In 2004, O'Rourke and colleagues reported the results of an evidence-based review on interventions used for stroke prevention. For CEA, the authors wrote: "Carotid endarterectomy of a symptomatic severe stenosis of an internal carotid artery remains one of the most effective methods of preventing recurrent stroke, reducing the risk by up to two thirds. The number-needed to-treat (NNT) to prevent 1 stroke at 2 years is 8 for high grade stenosis (\geq 70%) and 20 for moderate stenosis (\leq 50%–69%). Endarterectomy for asymptomatic stenosis of the internal carotid artery remains controversial. Although one study demonstrated a 53% relative risk reduction in ipsilateral stroke and death over 5 years, the number of events was small, with a higher NNT and men appeared to benefit considerably more than women. Long-term benefits may also be outweighed by the early risks of excess perioperative stroke or death (relative risk [RR] 6.52, 95% CI 2.66–15.96) and are influenced by the complication rates of individual surgeons. Guidelines suggest that surgery should be considered only for asymptomatic carotid disease if the complication rate is less than 3% and the stenosis is greater than 60%. The age and health of the patient, plaque stability and presence of coexisting cerebral artery disease should also be considered."⁶⁴

Halm EA, Chassin MR, Tuhrim S, et al. Revisiting the appropriateness of carotid endarterectomy. Stroke 2003;34:1464-1472.



CMS received position papers from various medical societies expressing support for expanded coverage for carotid artery stenting for the high-risk patient population. All professional societies were in favor of expanded coverage; however, there was considerable variation with respect to the specific patient population that would likely benefit from this treatment, how to identify that patient population, the degree of expertise/credentialing needed to perform stenting, and the need for a mandatory data collection as part of a national evaluation process.

The Society of Interventional Radiology (SIR): Supports expanded coverage for carotid stenting for patients at high risk for CEA, however SIR cautions that expanded coverage should be carefully limited to the right patient subgroup and recommends that the application of this technology to asymptomatic patients be restricted to patients with additional medical and anatomic conditions. With respect to physician competency and training, SIR in conjunction with ASITN (American Society of Interventional and Therapeutic Neuroradiology) and ASNR (American Society of Neuroradiology) drafted, "Quality Improvement Guidelines for the Performance of Cervical Carotid Angioplasty and Stent placement." According to SIR acceptable physician qualifications included but are not limited to: "Performance (under the supervision of a qualified physician and with at least 50% performed as the primary operator) of at least 200 diagnostic cervcicocerebral angiograms with documented acceptable indications and outcomes."67 As part of patient management SIR strongly suggests that CMS require an independent neurological evaluation pre-and post- stenting procedure. SIR advocates that facilities intending to provide carotid stenting have in place the same infrastructure required for CEA, appropriate imaging equipment and providers with substantial knowledge of cerebrovascular anatomy, knowledge of the clinical and imaging evaluation of patients with cerebrovascular disorders, including knowledge of the clinical manifestations and the natural history of cerebrovascular ischemic disease. Finally, SIR is supportive of mandatory outcomes reporting on a national level, to monitor patient outcomes.

The Society of Vascular Surgeons (SVS): Advocates the expansion of coverage, and recommends guarding against an over-proliferation of the procedure by creating an objective, independent, mandatory data collection mechanism. SVS, ACC (American College of Cardiology), SIR SCAI (The Society for Cardiovascular Angiography and Interventions) and SVMB (Society for Vascular Medicine and Biology) advocate that the carotid stenting registry should be audited and nationally monitored. With regard to physician training, SVS believes that physicians must have knowledge of all treatment options for extracranial cerebrovascular disease, and must demonstrate clinical competency as described in a SVS, ACC, ACP, SCAI, SVMB joint clinical competence statement on Vascular Medicine and Catheter-based Peripheral Vascular Interventions. With respect to physician expertise, the parties above believe, "To achieve clinical competence in carotid stenting, [SVS, ACC, ACP, SCAI, and SVMB] recommends performance of a minimum of 30 diagnostic cerebrovascular angiograms, 15 as a supervised primary operator, and a minimum of 25 supervised carotid interventions, at least half as primary operator." SVS supports independent neurological assessment by a neurologist or other care provider with NIH stroke scale training; however it does not recommend the immediate availability of an intra cranial neurointerventionalist for neuro-rescue.

The Society for Vascular Medicine and Biology (SVMB) & The Society for Cardiovascular Angiography and Interventions (SCAI) & Society for Vascular Surgery (SVS) & The American College of Cardiology (ACC): The above mentioned groups are in agreement with expanding coverage for carotid artery stenting and have expressed general consensus on the delineation of skills and expertise that would be required to perform carotid stenting. However the level of skills that these groups suggest differs considerably from those posited by the SIR, ASITN and ASNR in the "Quality Improvement Guidelines for the Performance of Cervical Carotid Angioplasty and Stent placement." SVS, ACC, SCAI and SVMB favor less stringent guidelines with respect to provider familiarity and experience with specifically cerebrovascular interventions. Their guidelines for performing carotid stenting are set forth in the "ACC/ACP/SCAI/SVMB/SVS Clinical Competence Statement on Vascular Medicine and Catheter-Based Peripheral Vascular Interventions." Finally, all groups strongly support of the creation of an evaluation process to help ensure good patient outcomes.

American Academy of Neurology (AAN): believes that stroke prevention is the sole indication for carotid stenting and that neurologic symptoms due to carotid disease are the primary indications for intervention. According to the AAN, neurologic symptoms due to carotid disease are difficult to discern from other neurologic ailments and therefore ANN strongly recommends that a neurologist or other physician with experience in the management of patients with cerebrovascular disease be a component in the evaluation of patient prior to the procedure. The AAN has endorsed the physician credentialing paper of the Neuroscience Coalition (comprised of The American Academy of Neurology (AAN), The American Association of Neurological Surgeons (AANS), The American Society of Interventional and Therapeutic Neuroradiology (ASITN), The American Society of Neuroradiology (ASNR), The Congress of Neurological Surgeons (CNS), the AANS/CNS Cerebrovascular Section, and the Society of Interventional Radiology (SIR)).

The American Society of Interventional and Therapeutic Neuroradiology (ASITN): is also in favor of expanded coverage for carotid artery stenting for high-risk patients. ASITN has also voiced concerns about the inappropriate use of this procedure on asymptomatic patients and maintains that medical therapy should be the standard of care for most patients with asymptomatic carotid stenosis. ASITN posits that medical therapy is the best treatment for the majority of patients with asymptomatic carotid artery stenosis and that neither CEA nor CAS should be offered to the majority of patients with asymptomatic carotid artery disease, especially in the absence of CAS trials "report[ing] morbidity and mortality rates approaching the 3% figure deemed to be necessary to achieved benefit from CEA in asymptomatic patients." Citing data from the ACAS, ACST and Cardiovascular Health study, ASITN believes that patients with asymptomatic carotid stenosis are rare (<.5% of the Medicare population) and have are known to have very low rates of stroke. According to the ASITN position, "Both ACAS and ASCT have definitively proved that there is NO increasing risk with increasing degrees of stenosis in asymptomatic patients." With respect to facility requirements to perform CAS, ASITN favors the JCAHO guidelines for Primary Stroke Centers based on the Brain Attack Coalition recommendations as a model for these requirements and recognizes the need for uniform data collection on patients' outcomes for this procedure.

7. Public Comments

A. Initial 30-Day Comment Period

After initiating the NCD process, the tracking sheet was posted marking the 30 day public comment period. During that time we received numerous comments supporting our intention to expand coverage for carotid artery stenting to high risk patients. While the comments were favorable, many commenters stressed the importance of ensuring that physicians were properly trained to perform carotid stenting. Additionally, a few commenters suggested that facilities intending to offer the procedure be high volume cardiac or vascular centers. Individual physicians, as well as those representing societies, suggested the levels of credentialing and experience physicians should have to perform carotid stenting. Comments ranged in specificity from naming the type of imaging equipment facilities should have in place to listing the number of procedures physicians should have performed prior to doing carotid stenting. There was some disparity amongst the different physician societies with respect to appropriate and adequate experience and prior interventional procedures required to successfully perform the procedure. Other comments included data on carotid stent trials by the manufacturers. Many cited inclusion criteria for these trials as factors that define the high risk patient population and also provided published articles intended to demonstrate the benefits of carotid stenting. For more details or to view the public comments please our website at: https://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=128

B. Final 30-Day Comment Period

CMS solicited public comments specifically relating to appropriate criteria /comorbid or chronic conditions for defining patients at high risk for CEA, criteria for appropriately defining symptomatic patients, professional and facility standards for performing PTA of the carotid artery with carotid stent placement, evaluation process for providers and facilities, and the overall CMS decision. During the 30-day comment period, CMS received 204 public comments totaling approximately 158 pages. Commenters included major national professional associations (e.g., neuroradiologists, cardiologists, vascular surgeons), device manufacturers national associations of health plans, academic researchers, practicing professionals, and other individuals including patients and caregivers. All commenters supported expanded coverage of carotid stents. There were 27 comments supporting the covered patient indications outlined in our proposed decision memorandum. Many commenters, however, did not agree completely with the proposed coverage and had additional concerns. These were taken into consideration in the final analysis. A summary of the comments is provided below.

Criteria for High Risk Patients: A total of 10 public comments received suggested that CMS broaden the current definition of high risk patients to be more reflective of the inclusion criteria from Category B IDE clinical trials and the high risk trials such as ARCHER, SAPPHIRE, and BEACH. Specifically, comments suggested that CMS incorporate additional medical and anatomical conditions that might qualify a person as high risk for surgery. CMS has modified the decision to include these additional conditions.

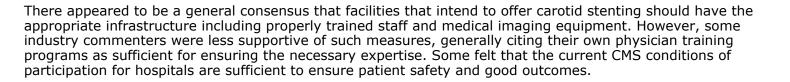
A few respondents were concerned by the language regarding determination of high risk status by a surgeon. Interventionalists generally argued that surgeons will be hesitant to declare a patient too risky for surgery and would therefore be likely to perform inappropriate surgeries on patients who might fare better with a carotid stent. Conversely, surgeons posited that interventionalists would self refer patients leading to a proliferation of unnecessary and inappropriate carotid stenting procedures. CMS will include conditions used to determine patients at high risk for CEA in the published CAS trials as listed in the decision section.

Criteria for Symptomatic Patients: A few comments endorsed the CMS proposed definition of symptoms of carotid artery stenosis: TIAs and amaurosis fugax. Also, there were some comments that voiced support of the limited coverage of symptomatic patients, noting that symptomatic patients with stenosis \geq 70 derive the greatest benefit from CAS. A total of 73 comments suggested expanding coverage to patients whose carotid artery stenosis ranges from 50% to 70%. Most comments addressing the symptomatic patient population emphasized that patients with \geq 50% stenosis would benefit from carotid stenting, based on evidence from clinical trial publications and the current FDA approved label indications for carotid stent systems. Commenters that disagreed with CMS's decision indicated that limiting the covered symptomatic patient population to only include those with \geq 70% runs counter to what FDA has already permitted as an appropriate indication/ patient population. According to these commenters, symptomatic patients with ulcerated plaques and with \geq 50% stenosis would benefit from undergoing CAS and asserted that selecting a cutoff of \geq 70% was not specifically supported by clinical trial data. These commenters argue that recent CAS clinical trials included symptomatic patients with stenosis greater than 50%.

CMS will provide coverage for symptomatic patients with carotid artery stenosis between 50% and 70% under the CMS clinical trials policy, the Category B IDE clinical trial policy, and the PMA study policy, as specified in the decision section of this memorandum. As noted in the analysis section, CMS believes the evidence does not support expanding coverage at this time for patients outside the controlled settings of clinical trials.

Coverage of Asymptomatic Patients: There were 123 comments which did not agree with CMS's decision to not provide broader coverage for asymptomatic patients. Again, comments pointed out that the FDA approved label for carotid stent systems includes the asymptomatic patient population. Medicare coverage of CAS with distal embolic protection is available for patients at high risk for surgery with asymptomatic carotid stenosis ≥ 80% under the CMS clinical trials policy and the PMA study policy. CMS disagrees with commenter suggestions that coverage of asymptomatic patients should be expanded beyond our existing settings. As noted in the analysis section, CMS's conclusion is based on the limited evidence on CAS for high risk patients with asymptomatic carotid stenosis.

Professional Standards and Facility Evaluation Process: Individual physicians as well as many professional societies such as SCAI, SVS, ASITN and SIR strongly supported a rigorous and systematic mechanism to ensure proper credentialing and competency for those physicians interested in performing CAS. In addition, some industry stakeholders offered to work with CMS to help create a data collection and monitoring process for facilities.



While many comments favored a national mechanism to monitor facilities and physicians for competency and expertise in performing carotid stenting procedures, there was little comment on which organization would take the lead on such a task, nor definitive plans proposed for implementation. Consequently, CMS has established minimum facility standards in this decision memorandum, along with a mechanism to document facility competency. CMS will continue to work with professional societies, industry and national quality assurance entities concerning appropriate standards.

VIII. CMS Analysis

National Coverage Determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act \S 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." \S 1862(a)(1)(A).

For this review of CAS, there were 5 randomized trials (CAVATAS, SAPPHIRE, 2 by Brooks et al., and 1 by Albert) and 5 published case-series, cohort or registry studies (CARESS, Cremonesi et al., Reimers et al., Roubin et al., SSYLVIA). The results of 5 other studies (ARCHER series, BEACH, CABERNET, CASCADE, MAVERIC II) have been presented at national meetings.

Of the trials, the two reported by Brooks had relatively small sample sizes and were conducted in one community hospital. The trial reported by Albert was terminated early due to a significantly higher rate of ipsilateral stroke, procedure-related death, or vascular death at the 1 year endpoint for patients undergoing CAS compared to CEA. CAVATAS was initially designed to study percutaneous transluminal (balloon) angioplasty to CEA. During the course of the trial, carotid stents became available and were then allowed as a treatment option. However, only 55 patients received a stent and the study was not specifically designed to fully evaluate CAS. The negative trial by Albert, the 2 trials by Brooks and CAVATAS provided only limited evidence on CAS. SAPPHIRE studied more patients (n= 334) but several issues have been raised about the trial and its results that may hamper generalizability outside the restrictive setting of a randomized trial. First, the patients that were randomized were highly selected. Of the 747 patients enrolled, only 334 were randomly assigned to the treatment groups. It is very unlikely this level of selectivity, where both a surgeon and an interventionalist must agree on treatment, will be available in actual practice outside a trial. The influence of this selection process is suggested by the results of the SAPPHIRE CAS registry, which showed a higher rate of major adverse events at 360 days for asymptomatic patients compared to asymptomatic patients in the randomized CAS treatment arm (15.7% versus 10.3%, respectively). 72 Also, physicians participating in trials usually have much more experience in study procedures than physicians in actual practice settings. These factors may significantly affect the observed health outcomes of CAS outside the realms of clinical trials.

Second, patients assigned CAS were also treated with clopidogrel (75 mg per day), which has been shown in randomized controlled trials to significantly reduce the risk of cardiovascular death, MI and stroke. 73,74 The actual length of treatment with clopidogrel was not reported in the SAPPHIRE publication, although it was likely at least 2 to 4 weeks for each patient as stated in the protocol. Since patients assigned to CEA were not treated similarly, the use of clopidogrel is a potential confounder. The actual duration of treatment with clopidogrel is an important variable that should be disclosed. Since there was no medical therapy control group, the independent effects of CAS with embolic protection or clopidogrel alone cannot be determined from the SAPPHIRE trial.

In addition, Cambria noted on the SAPPHIRE trial that "the small sample size and the study end points preclude major conclusions about the relative roles of endarterectomy and carotid-artery stenting in the treatment of carotid artery stenosis. Physicians, industry sponsors, and regulatory agencies should collectively insist on large-scale, multicenter trials in order to clarify the appropriate role of carotid artery stenting in patients in different clinical and anatomical subgroups. Such trials have been initiated in North America and Europe."75

Since all the above trials compared CAS to CEA, the fundamental assumption is that CEA is an appropriate treatment for patients in these trials. However, with advances in medical therapy and stroke prevention, the appropriateness of CEA for certain populations has been revisited. In addition, none of the CAS trials or studies included a medical therapy or control group. This situation presents a challenge in determining when to perform a procedure and when to continue best medical therapy. Optimal medical therapy has certainly changed since the trials on CEA have been completed. Estimates of stroke risk with medical therapy may have in turn changed. The influence of newer medications needs to be considered when determining the risks and benefits, and may, in many instances, reduce the appropriateness of any procedure. These issues will be discussed further in the following sections.

Since patients with symptomatic carotid artery stenosis and patients with asymptomatic carotid stenosis have different risk profiles, it would be important to consider the evidence for these groups separately for coverage.

- 1. Is the evidence sufficient to conclude that carotid artery stenting improves health outcomes for patients with symptomatic carotid artery stenosis and who are at high risk for CEA?
 - a. What degree of stenosis should be treated?

Patients with symptoms from carotid artery stenosis, such as TIAs, have "a substantial short-term risk of stroke, hospitalization for cardiovascular events and death." As noted above, all CAS trials have used CEA as the comparison group. Thus a basic understanding of CEA is important, as is a determination of when CEA is recommended. For patients with symptomatic stenosis, CEA has been shown in trials such as NASCET (first phase and second phase) and ECST to significantly reduce the risk of stroke in symptomatic patients with stenosis \geq 70%. In 1991, the NASCET (first phase) investigators reported that "risk of stroke and benefit from the procedure are greatest for symptomatic patients with at least 70% stenosis of the internal carotid artery." They further noted that "patients with 50 to 69% stenosis experience lesser benefit, and some other groups may even be harmed by carotid endarterectomy, including women and patients with transient monocular blindness only." 18

In 1998, the NASCET (second phase) investigators reported on a larger sample (n=2267) of symptomatic patients with moderate stenosis < 70% and found a modest reduction in ipsilateral stroke but no difference in deaths or total strokes. They stated: "Endarterectomy in patients with symptomatic moderate carotid stenosis of 50 to 69 percent yielded only a moderate reduction in the risk of stroke. Decisions about treatment for patients in this category must take into account recognized risk factors, and exceptional surgical skill is obligatory if carotid endarterectomy is to be performed." No benefits have been shown from CEA for patients with stenosis < 50% since the etiology of strokes in these patients is likely due to pathology in areas other than the carotid arteries.

In 1998, the ECST investigators reported the results of a randomized controlled trial on 3024 patients and noted that "on average, the immediate risk of surgery was worth trading off against the long-term risk of stroke without surgery when the stenosis was greater than 80% diameter." The investigators further noted that, "For the combined outcome of surgical events, ipsilateral major ischaemic strokes, and other major strokes, there was no overall effect below about 70-80% stenosis." 81

Since CEA has been shown to improve health outcomes for specific patient populations, CAS may be inferred to have similar benefits if found to be noninferior or equivalent to CEA. For symptomatic patients with carotid artery stenosis > 70%, there is evidence and agreement about the use of CEA. For CAS, SAPPHIRE studied 334 high risk patients (but only 96 high risk patients with symptomatic stenosis), and showed no significant differences between CAS and CEA for death, stroke, and MI at 360 days. The degree of stenosis was not reported in the SAPPHIRE trial. A trial conducted in a community hospital by Brooks and colleagues on symptomatic patients (n= 104) with stenosis > 70% showed that CAS and CEA had similar rates of death and cerebral ischemia. A trial by Albert (n=219) showed a significantly higher primary endpoint rate in patients who received CAS compared to CEA; however, the report was an abstract. A complete report of the trial has not been published therefore full consideration of this trial is not possible at this time. Several registry or cohort studies and evidence-based reviews provide supporting evidence for CAS and CEA. In 2004, O'Rourke and colleagues reported "carotid endarterectomy remains the definitive treatment in patients with symptomatic stenosis of the internal carotid artery of 70% or higher." In 2000, Gubitz and Sandercock reported "The benefit from surgery was related to the degree of stenosis. For people with severe stenosis (greater than 70% by angiography), surgery almost completely abolished the risk of ipsilateral stroke over several years."

In February 2005, the BlueCross BlueShield Association Technology Evaluation Center (TEC) published a technology assessment on CAS with distal embolic protection (DEP). The TEC reviewed the SAPPHIRE trial and major CEA trails and concluded: "Whether CAS with DEP improves health outcomes cannot be determined since available evidence is insufficient to permit conclusions." The TEC assessment also considered the findings and deliberations of FDA Advisory Panel meeting in April 2004 and shared our concerns with the SAPPHIRE trial.

Considering the evidence and clinical situation, there appears to be sufficient evidence to infer that CAS with embolic protection can improve health outcomes for patients with severe symptomatic stenosis \geq 70% who are also at high risk for CEA, if performed with the same expertise and rate of adverse events as demonstrated in the published clinical trials. Since patients with severe symptomatic stenosis \geq 70% are at high risk for stroke, carotid interventions to reduce the risk of stroke should be considered. Although the published studies on CAS have various potential biases, we feel that the need for an alternative treatment to CEA for patients who are truly at high risk for CEA should be factored into the coverage decision, unlike the BCBS TEC report which did not consider this circumstance. By not covering this group, symptomatic patients who also are at high risk for surgery may be left with no other treatment options. The risk benefit consideration may be similarly influenced. However, having mentioned this situation, the high risk CAS studies compared CAS to CEA and found that CEA can be performed as well as CAS in a group classified as high risk. Therefore, two comparable options exist for patients with symptomatic stenosis \geq 70% who are at high risk

Since all patients who received CAS with embolic protection in the major trials received clopidogrel, it should be considered for patients undergoing CAS appropriately, according to FDA recommendations.⁸⁹

For symptomatic patients with carotid artery stenosis < 70%, NASCET (second phase) showed a benefit in ipsilateral stroke for stenosis of 50-69% but no overall benefit for any stroke and death from any cause. As noted by the trial investigators (NASCET, ECST) and by authors of evidence-based reviews, there remain concerns about the risk and benefits of CEA for patients with symptomatic carotid stenosis of 50-69%. In 2004, Barnett note that "special caution must be exercised for patients with only moderate (50%-69%) stenosis who are women or who have had ocular symptoms only." In 2000, Gubitz and Sandercock reported: "People with moderate stenosis (50-70% by angiography) also benefited, although to a lesser extent, and it is generally thought that the risk of stroke is not great enough to make endarterectomy worthwhile in this group. Importantly, not all patients with operable lesions benefit from surgery; further research is ongoing to determine who might benefit most "91 In 1998, the NASCET investigators reported: "Many patients with symptomatic stenosis of less than 70 percent will not be considered appropriate candidates for endarterectomy when the risks and benefits are carefully weighted. Our final results do not justify a large increase in the rate of endarterectomy. We recommend restraint."92

The NIH sponsored, Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) is ongoing and should provide additional evidence on CEA and CAS, especially for patients with symptomatic stenosis of 50-69%, and the risk associated with any procedure. $\frac{93}{2}$ CREST was designed as a prospective, randomized trial of carotid endarterectomy (CEA) versus carotid artery stenting (CAS) as prevention for stroke in patients with symptomatic stenosis \geq 50%, and has a targeted sample size of 2500 patients, more than all prior trials combined. Several other trials on CEA and CAS (ICSS, EVA-3S, SPACE) are also ongoing.

Based on the current evidence for patients with symptomatic stenosis of 50-69%, the fundamental question of whether CEA should be performed for these patients has not been answered. If CEA cannot be generally recommended, then CAS, in turn, cannot be generally recommended. Thus, there is insufficient evidence for patients with symptomatic carotid artery stenosis < 70%. The BCBS TEC reported: "Whether CAS with DEP is as beneficial as either CEA or optimal medical management for high surgical risk patients cannot be determined since available evidence is insufficient to permit conclusions." This is also consistent with the recommendations of a Cochrane evidence-based review by Coward and colleagues who reported: "The data available were limited. The overall estimates of effect were both imprecise and difficult to interpret because of substantial heterogeneity. The data were therefore insufficient to support a change from routine clinical practice in the types of patients for which carotid endarterectomy is the current standard treatment. The data support the continuing inclusion of patients within randomized clinical trials between endovascular and surgical treatment for carotid artery stenosis." stenosis."

While we await the completion of ongoing clinical trials such as CREST, ICSS, EVA-3S and SPACE, coverage for CAS with embolic protection for high risk patients with symptomatic carotid artery stenosis of 50-69% may be available under the IDE clinical trials policy or FDA required, post market approval studies.

2. Is the evidence sufficient to conclude that carotid artery stenting improves health outcomes for patients with asymptomatic carotid artery stenosis > 80% and who are at high risk for CEA?

Patients with asymptomatic carotid artery stenosis have a different risk profile than patients with symptoms. Asymptomatic patients with hemodynamically significant carotid artery stenosis have an annual stroke event rate of 2-5% (about 2% stroke occurrence per year among controls in ACST). $\frac{96,97}{1}$ In contrast, about 10.5% of patients with symptoms, such as a TIA, will have a stroke in the short term. $\frac{98}{1}$ While CEA has been well accepted for patients with symptomatic carotid artery stenosis \geq 70%, there remains controversy for asymptomatic patients, due, in part, to the lower event rates and the development of medications, such as antiplatelet and lipid lowering drugs, for stroke prevention.

The evidence on CEA for patients with asymptomatic carotid artery stenosis was obtained mainly from the Veterans Affairs study, MACE, ACAS and ACST. The Veterans Affairs Cooperative Study did not demonstrate any significant differences in strokes and deaths between the CEA group and the optimal medical therapy group. MACE was terminated early due to a significantly higher number of MIs and TIAs in the CEA group compared to the medical group.

The ACAS and ACST showed benefits but the investigators of both these trials expressed restraint in their conclusions and targeted specific individuals. The ACAS committee reported that "patients with asymptomatic carotid artery stenosis of 60% or greater reduction in diameter and whose general health makes them good candidates for elective surgery will have a reduced 5-year risk of ipsilateral stroke if carotid endarterectomy performed with less than 3% perioperative morbidity and mortality is added to aggressive management of modifiable risk factors."99 The ACST investigators reported that "in asymptomatic patients younger than 75 years of age with carotid diameter reduction about 70% or more on ultrasound (many of who were on aspirin, antihypertensive, and in recent years, statin therapy), immediate CEA halved the net 5-year stroke risk from about 12% to about 6% (including the 3% perioperative hazard)."100 They further stated that "outside trials, inappropriate selection of patients or poor surgery could obviate such benefits."101

Even to a greater degree than for patients with symptomatic stenosis 50-69%, the controversy over CEA in asymptomatic patients has been noted in evidence-based reviews, guidelines and recommendations. In 2000, Gubitz and Sandercock reported that "a systematic review of all of the available randomized data shows that the efficacy of surgery for carotid stenosis without symptoms remains unproved and that further randomized trial evidence is needed; trials are ongoing."102 In 2003, Halm and colleagues conducted a meta-analysis of CEA clinical trials and reported that "although overall complications rates were low, rates among asymptomatic patients with high comorbidity exceeded recommended thresholds."103 In 2004, Brott and colleagues stated that "best medical treatment alone in high-risk asymptomatic patients may be superior to revascularization."104

In 2004, O'Rourke and colleagues reported that "we do not currently recommend surgery for asymptomatic disease, preferring to treat proven vascular risk factors aggressively with immediate follow-up in the event of any stroke symptoms." In 2004, Barnett noted in a commentary on the ACST: "Before concluding that the route has been cleared to the operating room for most patients with asymptomatic carotid stenosis, several factors require careful consideration. First, patients must recognize that with good medical care they face only a 2% annual stroke rate, which falls below 1% after successful carotid endarterectomy. But the benefits will exceed the risks only if the operative hazards remain low, otherwise they could be obliterated. Contemporary reports suggest that the rates of operative complications often exceed by 1 or 2% the low rates achieved by trial surgeons (3%).6,7 Thus, if such surgery is to be offered, audited results of surgeon's operative records should be readily available to referring physicians and patients. Institutions and departments should require totally independent audits of surgical morbidity rates and ensure their ready availability." 106

In 2004, Barnett further reported in an evidence-based commentary on carotid endarterectomy (CE in this excerpt): "Two large trials involving asymptomatic patients have presented evidence that there is modest benefit favoring CE in subjects with stenosis but no symptoms, provided that highly skilled surgeons are involved and that complication rates are below 3%. Even with this low operative complication rate, the number needed to treat to prevent 1 stroke in 2 years is 83. In the 2 large trials involving a total of nearly 4500 patients, the annual stroke and death rate after CE was 1%, versus 2% among those without CE. What we do not know is whether this 2% could be reduced by a strictly supervised regimen of best modern medical care, including control of blood pressure, diabetes mellitus, lipids and cigarette smoking, along with appropriate ASA therapy. A trial of CE versus tightly controlled (as opposed to standard) medical care is one of the last remaining major trials still required to complete our knowledge of the role of CE in stroke prevention in asymptomatic patients." 107

For CAS with embolic protection, SAPPHIRE studied 237 high risk patients with asymptomatic carotid artery stenosis > 80%. There were no statistically significant differences in the 30 day major adverse event rates and the 360 day major adverse event rates between CAS with embolic protection and CEA (6.0% versus 9.6% at 30 days; and 19.2% and 10.3% at 360 days, respectively). 108 However, patients who received CAS had almost twice as many 360 day major adverse events, a clinically important observation that needs further evaluation. As noted above, there were several factors with the SAPPHIRE trial that may hamper generalizability, such as the relatively small sample size, patient selection, physician experience, and lack of a medical therapy group. These factors may lead to a much higher rate of major adverse events in actual practices than seen in SAPPHIRE, creating a situation where the risks outweigh the benefits of CAS, especially for asymptomatic patients who have, in general, a lower natural stroke rate than patients with severe symptomatic stenosis.

Additional evidence on CAS for patients with severe asymptomatic stenosis should also be forthcoming. The CARESS Phase II trial should provide important data and evidence on risks and benefits of CAS in this population. The CARESS Phase II trial was designed "to assess the equivalence of the procedures in nonrandomly but concurrently assigned reverse ratios of 2,000 CSS patients to 1,000 CEA patients." The primary endpoint will be the combined rate of all-cause mortality and non-fatal stroke at 48 months. Patients with symptomatic stenosis > 50% and asymptomatic stenosis > 75% will be included.

Overall, there remains considerable controversy on the risks, benefits and appropriateness of carotid interventions for patients with asymptomatic carotid artery stenosis. This controversy was also noted in the public comments we received. Both sides of the debate submitted strongly held views. In general as noted by Barnett, patients with asymptomatic carotid stenosis who received good medical care are at low risk for stroke. Complication rates in actual practice from CEA often may exceed the reduction in risk from surgery. Although SAPPHIRE indicated that CAS was not inferior to CEA, the appropriateness of any procedure, CAS or CEA, remains unclear. In addition, relatively few patients with asymptomatic stenosis have been studied in CAS randomized trials. No trial has evaluated long term outcomes. No trial has compared CAS to optimal medical therapy. These types of trials are much needed and should be completed.

Based on currently available evidence, we believe that there is insufficient evidence to conclude that CAS with embolic protection improves health outcomes for patients with severe asymptomatic carotid artery stenosis > 80% and who are at high risk for CEA when performed outside the clinical trial setting. The BCBS TEC assessment that reported: "Whether CAS with DEP is as beneficial as either CEA or optimal medical management for high surgical risk patients cannot be determined since available evidence is insufficient to permit conclusions." 110 Additional evidence is needed. As noted earlier, CMS is interested in facilitating the completion of current and planned clinical trials and studies on CAS with distal embolic protection, such as FDA-required post approval studies. The additional evidence from these trials is extremely important in substantiating the short term outcomes of the prior CAS studies and in developing the evidence base on long term outcomes, especially for asymptomatic patients. Thus, CMS will provide coverage for patients with severe asymptomatic carotid artery stenosis > 80% who are also at high risk for surgery in IDE clinical trials and FDA-required post approval studies. By providing defined coverage, CMS also aims to provide an acceptable mechanism for patients to safely receive treatment in carefully controlled settings given the limited available evidence.

High Risk Definition

CMS has determined that patients at high risk for CEA are defined as having significant comorbidities and/or anatomic risk factors (i.e., recurrent stenosis and/or previous radical neck dissection), and would be poor candidates for CEA in the opinion of a surgeon. Significant comorbid conditions include but are not limited to CHF class III/IV, left ventricular ejection fraction < 30%, unstable angina, contralateral carotid occlusion, recent MI, previous CEA with recurrent stenosis, prior radiation treatment to the neck, and other conditions that were used to determine patients at high risk for CEA in the prior carotid artery stenting trials and studies, such as ARCHER, CABERNET, SAPPHIRE, BEACH, and MAVERIC II. This reflects the body of the evidence that flows from the inclusion and exclusion criteria of the high risk carotid stenting trials. For example, in the SAPPHIRE trial, separate stent and CEA registry arms were included for patients who met the entry criteria but were determined to be at too high risk for surgery by the vascular surgeon. In the randomized portion of the trial patients meeting all eligibility criteria were either randomized to treatment by stent or CEA, or placed into a stent or CEA registry, based on the medical judgment of the interventionalist and surgeon.

Provider Credentials and Facility Standards

Provider training and credentials are extremely important in ensuring that only competent physicians are performing CAS with embolic protection. More than most other invasive procedures, there is also a substantial learning period for carotid endovascular procedures. As with all other surgeries and procedures, the primary responsibility to assure that physicians who perform CAS with embolic protection have appropriate qualifications, high quality training and are competent to perform these procedures resides with the facilities where the procedures will be performed. However, CMS believes the training and experience required for CAS should be as rigorous as the training and experience required for coronary interventions, such as coronary artery stenting. Physician qualifications should be fully documented and maintained in the hospital record keeping system. Provider volume is an important factor for many procedures such as CEA and most likely CAS as well.

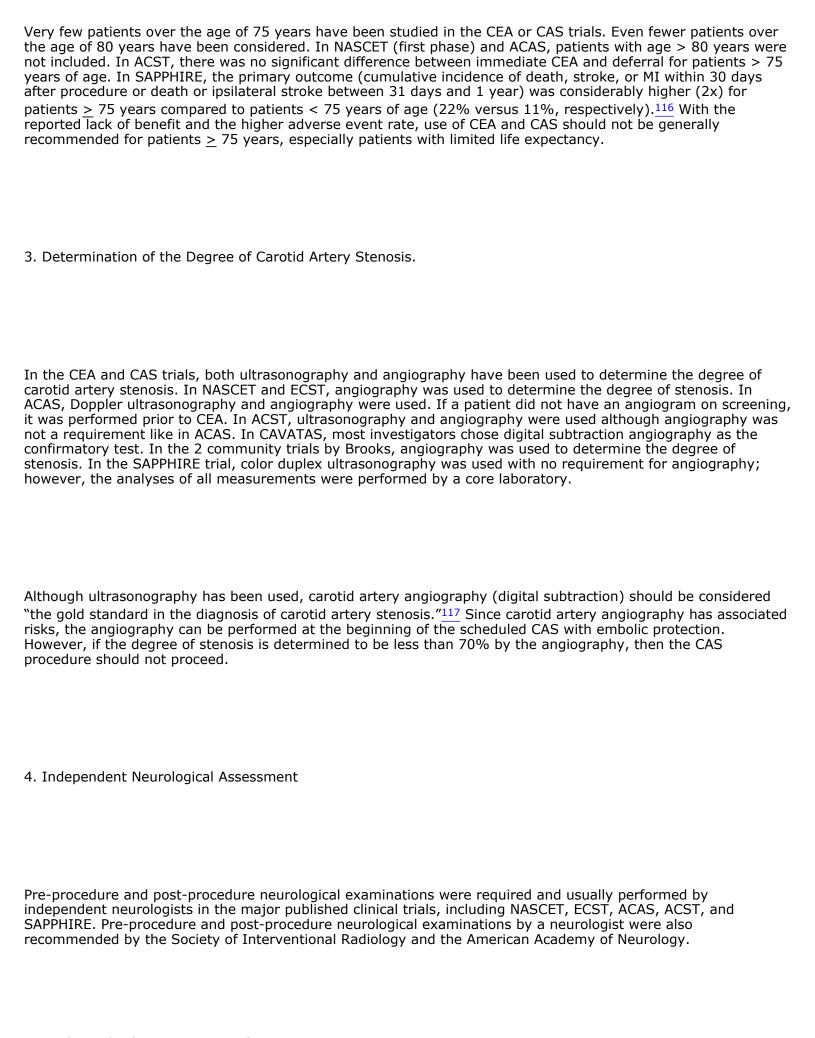
Each facility should have a clearly delineated program for granting carotid stent privileges and for monitoring the quality of the individual interventionalists and the program as a whole. The oversight committee for this program should be empowered to identify the minimum case volume for an operator to maintain privileges, as well as the (risk-adjusted) threshold for complications that the institution will allow before suspending privileges or instituting measures for remediation. 111 Committees are encouraged to apply published standards from national specialty societies recognized by the American Board of Medical Specialties 12 to determine appropriate physician qualifications.

Facilities that provide CAS with embolic protection should have appropriate staff and facilities for performing this service. Access to a state of the art intervention suite that includes adequate monitoring equipment and availability of emergency medical personnel should be available. For CEA, Barnett reported that "low-volume hospitals with high complication rates would be wise to refer appropriate patients for endarterectomy to hospitals with more experienced surgeons." This should likewise apply to CAS with embolic protection.

CMS believes that the professional staff, infrastructure and support system available at facilities intending to offer carotid stenting procedures are critical in ensuring good patient outcomes. These are the elements that will likely factor into the appropriate assessment of the patient's suitability for surgery or stenting and the successful placement of the stent and required follow up care.

Facilities and providers that routinely and repeatedly perform this procedure and follow patients for long periods of aftercare have a greater chance of successful outcomes. The volume necessary to achieve this goal is not presently known. Due to the potentially significant morbidity and mortality of this procedure and the learning curve necessary for optimal performance, CMS requires that all facilities performing this procedure for Medicare beneficiaries to demonstrate competency.

IX. Other Factors to Consider
Although these are not specific coverage requirements, there are several important factors to consider in the application and practice of carotid artery stenting such as:
1. Stroke Prevention
Optimal medical therapy remains a crucial aspect of stroke prevention for all patients, especially patients with asymptomatic carotid artery stenosis. Brott and colleagues noted that "better antihypertensive treatments, including the availability of ACE inhibitors and ACE receptor antagonists, improved antiplatelet regimens, potential for tighter glucose control in diabetes, and well-tolerated lipid-lowering regimens provide a potent armamentarium for the medical approach to treatment of asymptomatic carotid artery disease in high-risk patients." 114
Since all patients who underwent CAS with embolic protection in the major trials received clopidogrel, it should be administered to all patients appropriately, according to FDA recommendations. $\frac{115}{2}$
Behavior modifications with smoking cessation and adequate physical activity are also important, as well as increasing awareness of stroke warning signs.
2. Age and Life Expectancy



X. Conclusions

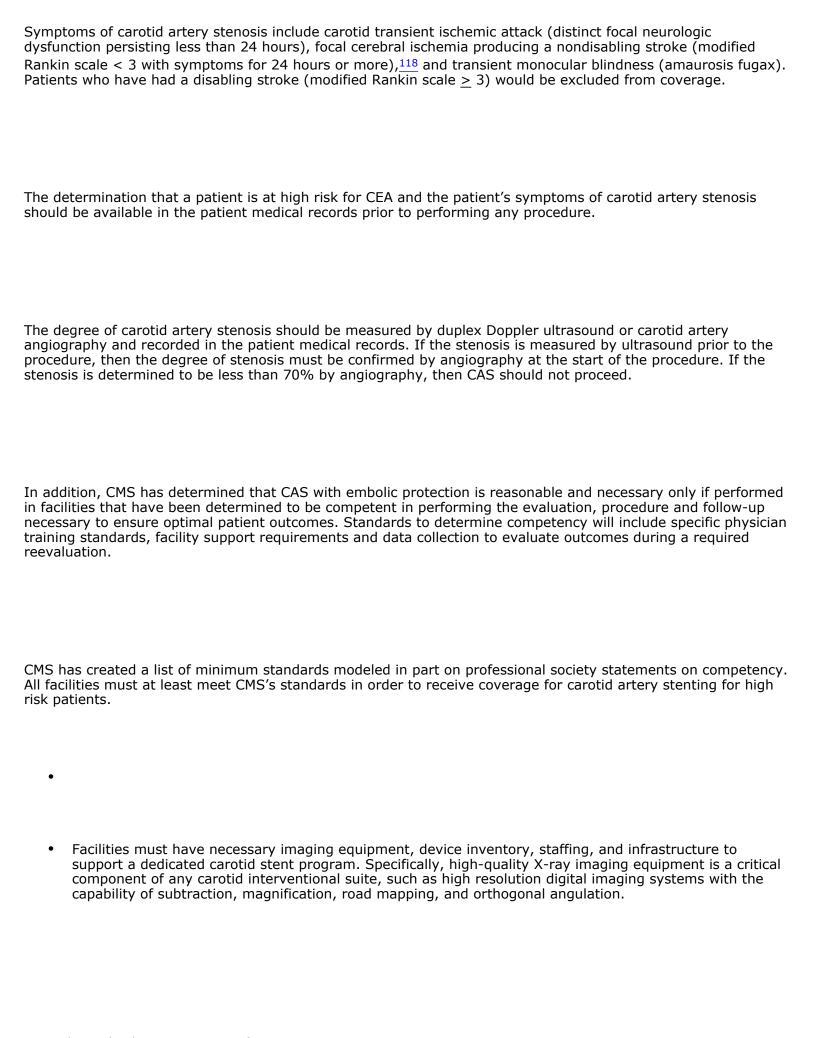
Stroke causes significant morbidity and mortality for the Medicare population. Procedures such as CEA and CAS have been used to improve health outcomes in specific subpopulations. However, these procedures carry considerable risks that may outweigh the benefits in many patients. A thorough consideration of the risks and benefits is needed to help make an informed decision on the choices of therapy. Stroke prevention with appropriate therapy must be optimized and recommended. Other considerations such as smoking cessation and life style modifications are also important.

The Centers for Medicare and Medicaid Services (CMS) has determined that the evidence is adequate to conclude that carotid artery stenting (CAS) with embolic protection is reasonable and necessary for the following:

- 1. Patients who are at high risk for carotid endarterectomy (CEA) and who also have symptomatic carotid artery stenosis > 70%. Coverage is limited to procedures performed using FDA approved carotid artery stenting systems and embolic protection devices;
- 2. Patients who are at high risk for CEA and have symptomatic carotid artery stenosis between 50% and 70%, in accordance with the Category B IDE clinical trials regulation (42 CFR 405.201), as a routine cost under the clinical trials policy (Medicare NCD Manual 310.1), or in accordance with the National Coverage Determination on CAS post approval studies (Medicare NCD Manual 20.7);
- 3. Patients who are at high risk for CEA and have asymptomatic carotid artery stenosis ≥ 80%, in accordance with the Category B IDE clinical trials regulation (42 CFR 405.201), as a routine cost under the clinical trials policy (Medicare NCD Manual 310.1), or in accordance with the National Coverage Determination on CAS post approval studies (Medicare NCD Manual 20.7).

Patients at high risk for CEA are defined as having significant comorbidities and/or anatomic risk factors (i.e., recurrent stenosis and/or previous radical neck dissection), and would be poor candidates for CEA in the opinion of a surgeon. Significant comorbid conditions include but are not limited to:

- congestive heart failure (CHF) class III/IV;
- left ventricular ejection fraction (LVEF) < 30%;
- unstable angina;
- contralateral carotid occlusion;
- recent myocardial infarction (MI);
- previous CEA with recurrent stenosis;
- prior radiation treatment to the neck; and
- other conditions that were used to determine patients at high risk for CEA in the prior carotid artery stenting trials and studies, such as ARCHER, CABERNET, SAPPHIRE, BEACH, and MAVERIC II.



•	Advanced physiologic monitoring must be available in the interventional suite. This includes real time and archived physiologic, hemodynamic, and cardiac rhythm monitoring equipment, as well as support staff who are capable of interpreting the findings and responding appropriately.
•	Emergency management equipment and systems must be readily available in the interventional suite such as resuscitation equipment, a defibrillator, vasoactive and antiarrhythmic drugs, endotracheal intubation capability, and anesthesia support.
•	Each institution should have a clearly delineated program for granting carotid stent privileges and for monitoring the quality of the individual interventionalists and the program as a whole. The oversight committee for this program should be empowered to identify the minimum case volume for an operator to maintain privileges, as well as the (risk-adjusted) threshold for complications that the institution will allow before suspending privileges or instituting measures for remediation. 119 Committees are encouraged to apply published standards from national specialty societies recognized by the American Board of Medical Specialties 120 to determine appropriate physician qualifications. Examples of standards and clinical competence guidelines include those published in the December 2004 edition of the American Journal of Neuroradiology 121, and those published in the August 18, 2004 Journal of the American College of Cardiology. 122
•	To continue to receive Medicare payment for CAS under this decision, the facility or a contractor to the facility must collect data on all carotid artery stenting procedures done at that particular facility. This data must be analyzed routinely to ensure patient safety, and will also be used in the process of recredentialing the facility. This data must be made available to CMS upon request The interval for data analysis will be determined by the facility but should not be less frequent than every 6 months.
Since evalua followi	there currently is no recognized entity that evaluates CAS facilities, CMS has established a mechanism for ating facilities. Facilities must provide written documentation to CMS that the facility meets one of the ing:
1.	The facility was an FDA approved site that enrolled patients in prior CAS IDE trials, such as SAPPHIRE, and
2.	ARCHER; The facility is an FDA approved site that is participating and enrolling patients in ongoing CAS IDE trials,
3.	such as CREST; The facility is an FDA approved site for one or more FDA post approval studies; or

4. The facility has provided a written affidavit to CMS attesting that the facility has met the minimum facility standards. This should be sent to: Director, Coverage and Analysis Group 7500 Security Boulevard, Mailstop C1-09-06 Baltimore, MD 21244.
The letter must include the following information: Facility's name and complete address; Facility's Medicare provider number; Point-of-contact for questions with telephone number; Mechanism of data collection of CAS procedures; and, Signature of a senior facility administrative official.
A list of certified facilities will be made available and viewable at http://www.cms.hhs.gov/coverage/carotid-stent-facilities.asp . In addition, CMS will publish a list of approved facilities in the Federal Register. A new affidavit is required every two years to ensure that facilities maintain high standards.
All other Medicare policies on PTA of the carotid artery apply.
Appendix I [PDF, 112KB]
Appendix II
General Methodological Principles of Study Design (Section VI of the Decision Memorandum)
We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.
The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

1. Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were
 assigned (intervention or control). This is important especially in subjective outcomes, such as pain or
 quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by
 either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials

- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

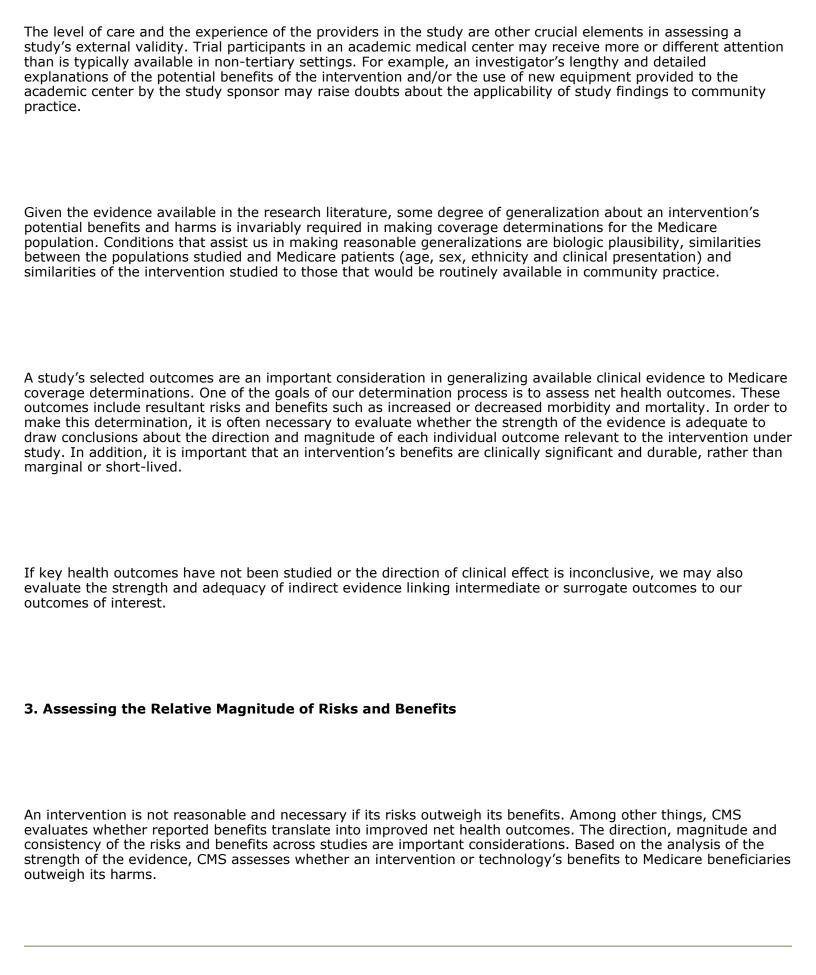
When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

2. Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies and type of outcome and length of follow-up.



 $\frac{1}{2}$ Wilson et al., 2002.

Modified Rankin Stroke Scale 0 - No symptoms at all. 1 - No significant disability despite symptoms; able to carry out all usual duties and activities. 2 - Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance. 3 - Moderate disability; requiring some help, but able to walk without assistance. 4 - Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance. 5 - Severe disability: bedridden, incontinent, and requiring constant nursing care and attention.
² Facility guidelines based on Clinical Competence Statement on Carotid Stenting: Training and Credentialing for Carotid Stenting Multispecialty Consensus Recommendations 2004 Society for Cardiovascular Angiography and Interventions; Society for Vascular Medicine and Biology; and Society for Vascular Surgery.
3 ABMS at http://www.abms.org/approved.asp.
⁴ Connors et al., 2004. "Training, Competency, and Credentialing Standards for Diagnostic Cervicocerebral Angiography, Carotid Stenting, and Cerebrovascular Intervention"
5 Creager et al., 2004.
6 Medicare NCD Manual Section 20.7.
7 American Heart Association, 2004.

8 Topol, editor, 2002.



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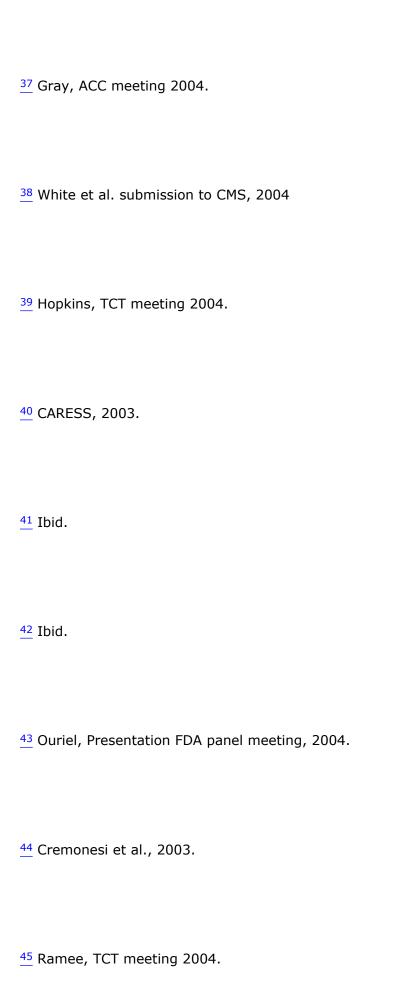
¹⁹ FDA is not bound by this Advisory Panel's recommendations.
Letter dated August 30, 2004 from Center for Devices and Radiological Health of the Food and Drug Administration (FDA) to Guidant Corporation http://www.fda.gov/cdrh/pdf4/P040012a.pdf
²¹ Federal Register Vol 68, No.187, September 26, 2003 p55,636.
22 Deek, 2001.
BlueCross BlueShield Association, 2005 at http://www.bcbs.com/tec/Vol19/19_15.pdf.
²⁴ Ibid.
²⁵ Albert, 2001.
²⁶ Albert, 2001.

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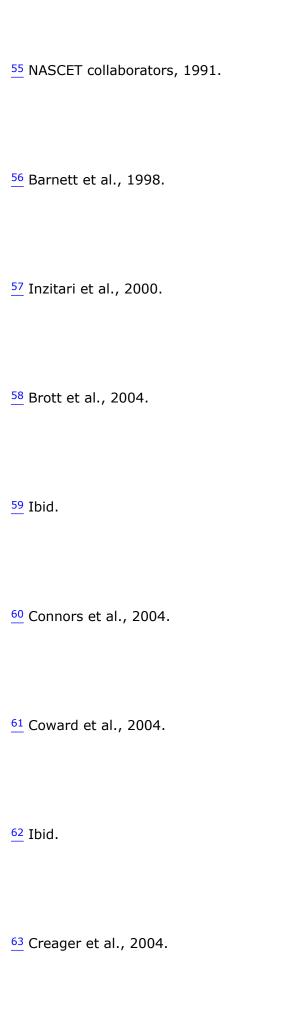
27 Brooks et al., 2004.

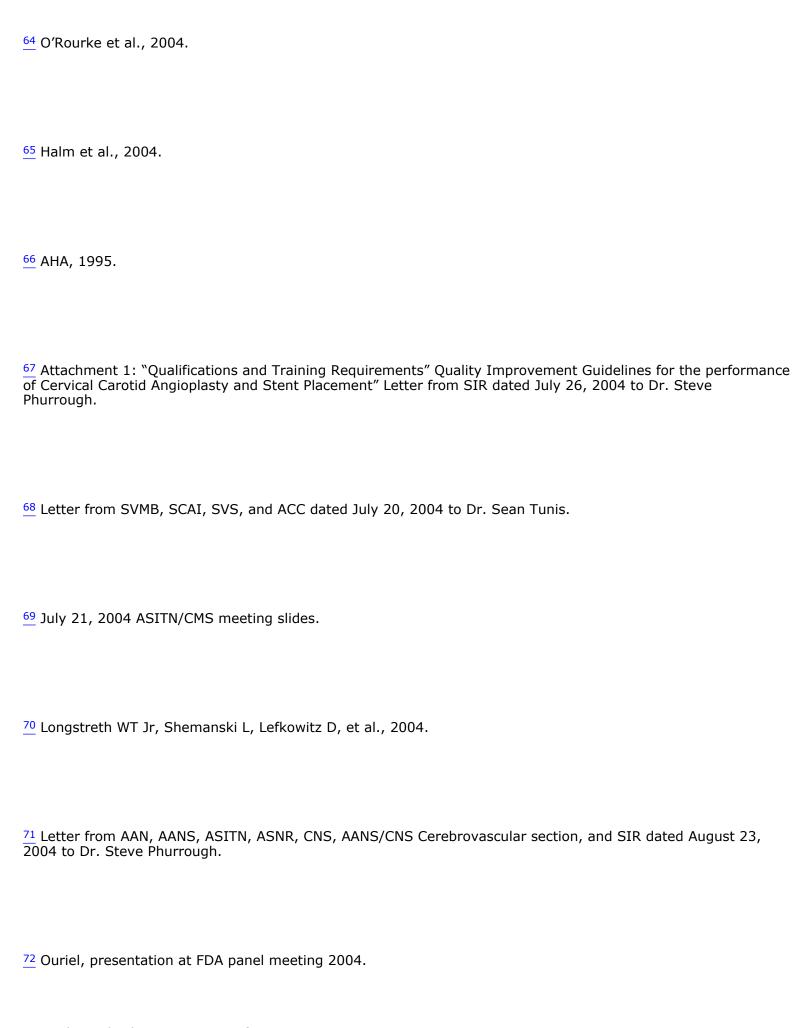


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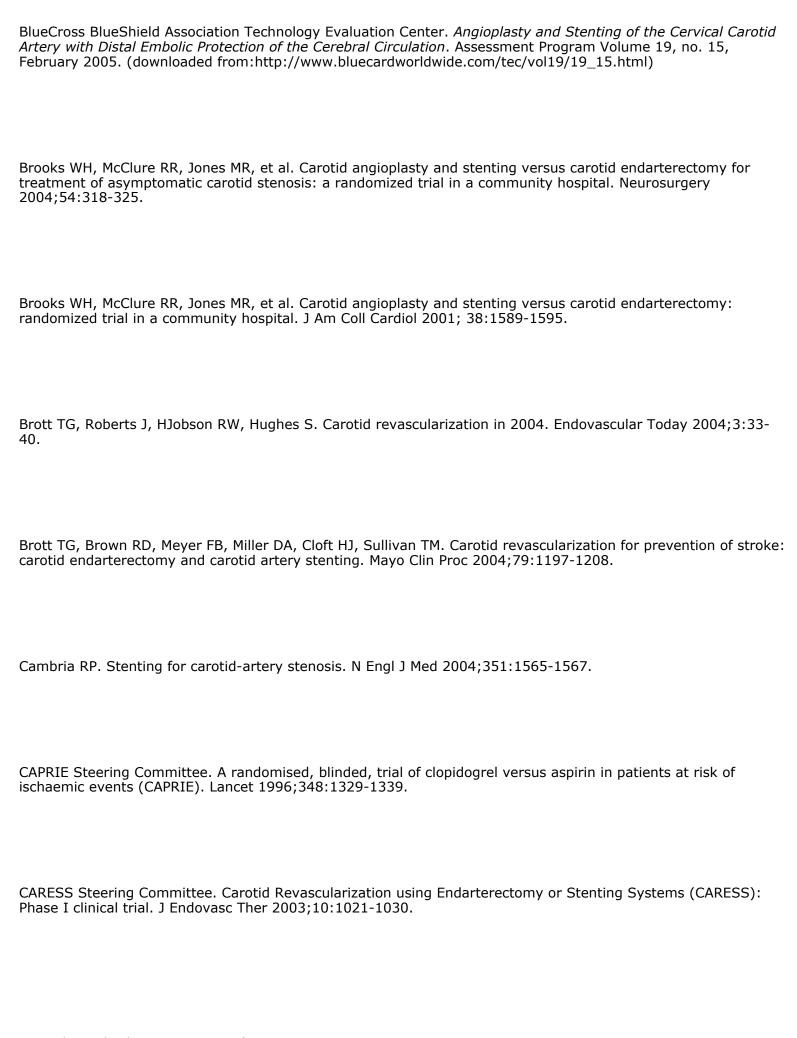
110 BCBS TEC, 2005.
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112 ABMS at http://www.abms.org/approved.asp.
113 Barnett, 2004.
114 Brott et al., 2004.
115 FDA NDA 20-839, 2002.
116 SAPPHIRE data submitted by Cordis.
<u>117</u> Yurdakul et al., 2004.

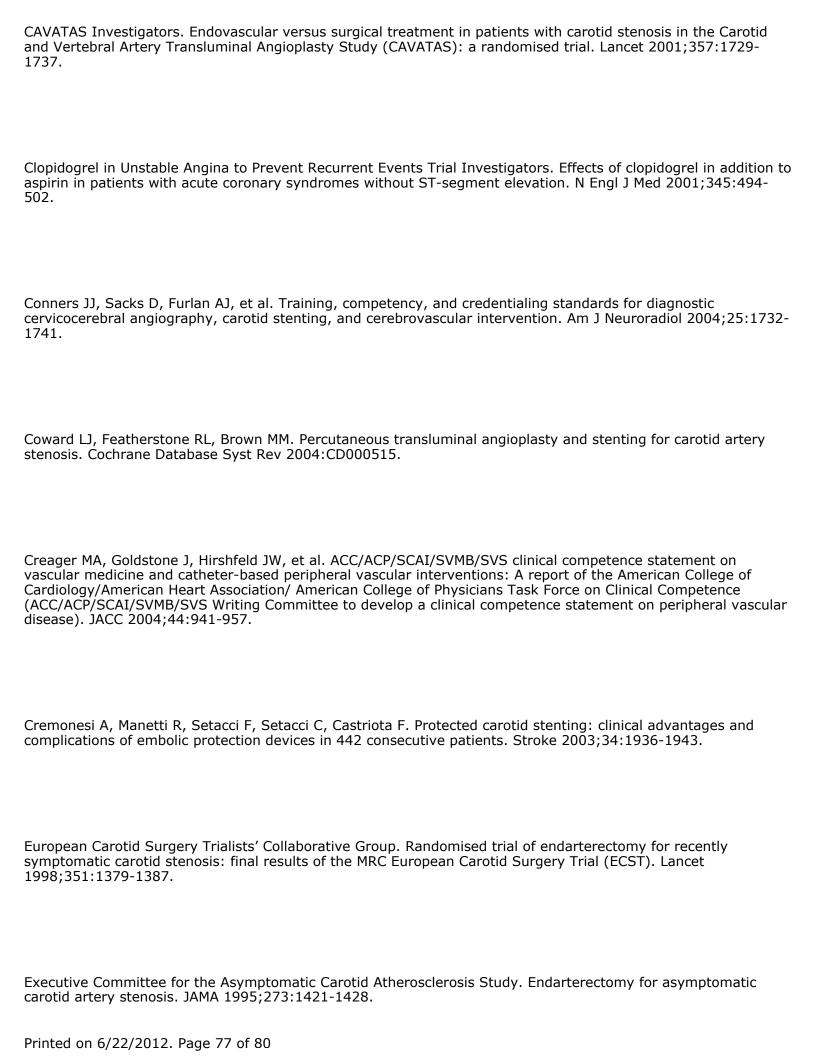
118 Wilson et al., 2002.
Modified Rankin Stroke Scale 0 - No symptoms at all.
 1 - No significant disability despite symptoms; able to carry out all usual duties and activities. 2 - Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance. 3 - Moderate disability; requiring some help, but able to walk without assistance. 4 - Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance. 5 - Severe disability: bedridden, incontinent, and requiring constant nursing care and attention.
¹¹⁹ Facility guidelines based on Clinical Competence Statement on Carotid Stenting: Training and Credentialing for Carotid Stenting Multispecialty Consensus Recommendations 2004 Society for Cardiovascular Angiography and Interventions; Society for Vascular Medicine and Biology; and Society for Vascular Surgery.
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123 Medicare NCD Manual Section 20.7.
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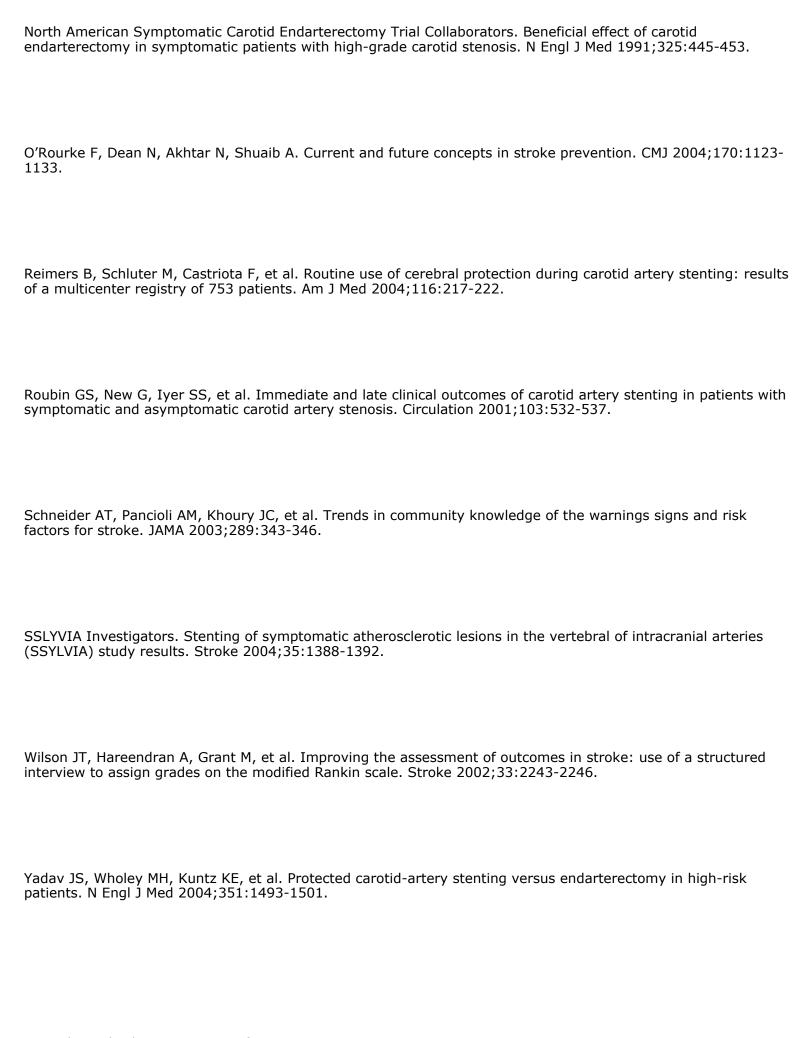
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